The effect of wet granulation on the physico-mechanical characteristics of microcrystalline cellulose

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THE EFFECT OF WET GRANULATION ON THE PHYSICO-MECHANICAL CHARACTERISTICS OF MICROCRYSTALLINE CELLULOSE

submitted by

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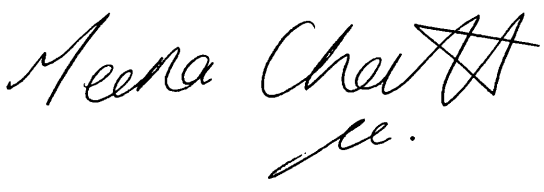

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To my parents and Varinder

for their constant love

and support

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Summary

The effect of wet granulation and granulation process variables on the physico-mechanical characteristics of microcrystalline cellulose (MCC) were studied. In most cases wet granulation was found to substantially reduce the compactibility of MCC. The reduction in compactibility was generally accompanied by a decrease in particle porosity, specific surface area available to adsorb nitrogen, and fribailiity, and was also accompaied by an increase in bulk density and friability. However, granule particle size distttribution was found to have a relatively minor effect on granule compactibility. Granule properties, including compactibility, were also found to be influenced by the amount of granulating fluid employed, the duration and rate of wet mass agitation, wet mass storage time before drying, and granule drying technique. Further, granule de-watering by solvent exchange was found to have a benificial effect on granule compactibility.

The theory that granulation reduced MCC compactibility by increasing intraparticle hydrogen bonding was developed. This phenomenon was termed quasi-hornification. However, unlike hornification of cellulose fibres described elsewhere, quasi-hornification of MCC observed in the present study did not reduce the ability of MCC to adsorb water vapour. Microcalorimetry indicated that during adsorption of water vapour by granulated MCC the extent of intraparticle bond disruption was greater than occurring during water vapour adsorption by ungranulated MCC. This provided limited evidence to support the theory that granulation resulted in increased intraparticle hydrogen bonding, some of which was reversible on adsorption of water vapour.

Wet granulation was found to have only a minor effect on the solubility parameters of MCC. Further, wet granulation did not alter the X-ray diffraction pattern and the Raman and ^{13}C-NMR spectra of MCC. However, as a result of granulation, the infra-red spectra of MCC obtained using the technique of attenuated total reflectance spectroscopy was altered slightly.

The inclusion of additive materials in the granulation fluid was studied in order to investigate their effect on MCC granule compactibility. In the case of some additives, notably ungelatinised starch and sodium lauryl sulphate, the compactibility of MCC was found to be slightly improved. Such improvements were considered at least partly due to the ability of such additives to reduce MCC quasi-hornification.

CONTENTS

Chapter 1. Introduction

Chapter 1. INTRODUCTION

1.1 Tablet formulation and manufacture

1.1.1 Desirable formulation characteristics

The compressed tablet is widely used for the administration of drugs via the oral route; Wells & Aulton (1988) reported that 45.8% of the dosage form types manufactured in the United Kingdom were tablets. However, probably at least 90% of all marketed drugs are available in tablet form.

The primary objective of a dosage form is the delivery of the correct amount of a pharmacologically active principle in a safe and effective manner (Banker & Peck, 1980). In order to comply with this and other requirements, the active principle must possess adequate chemically stability in the dosage form, and the tablets must exhibit acceptable weight and content uniformity together with suitable dissolution characteristics following administration (Sheth et al, 1980; Banker & Anderson, 1986; Rubinstein, 1988). In addition, it is highly desirable for tablets to be sufficiently robust so as to ensure product integrity prior to administration. The formulation should also allow production on a commercial scale with the desired consistency of product quality (York, 1988). For the vast majority of actives, the production of tablets exhibiting acceptable characteristics according to the above criteria cannot be achieved simply by compression of the active alone. Hence pharmacologically "inert" additives, collectively known as excipients, are combined with the active, and the formulation processed using appropriate techniques prior to compaction into the final tablet (Sheth et al 1980; Banker & Anderson, 1986; Rubinstein, 1988). The major class of excipient type is the fillers or diluents which may be added to increase the bulk of the tablet and to improve formulation compactibility and flow. Other classes of excipients include wet granulation binders for use in wet granulated formulations, disintegrants, and anti-friction excipients which include lubricants and glidants.

1.1.2 Methods of powder processing prior to compaction

1.1.2.1 Multi-operation processing - Granulation

Frequently granulation or particle agglomeration is performed in order to improve the fluidity and compactibility of a formulation and to reduce the segregation tendencies of its components (Record, 1980; Kristensen & Schaefer,

1987; Schwartz, 1988). A description of various wet granulation techniques including granulation by wet massing and screening, fluidised bed granulation, spray drying, or by extrusion and pelletisation / spheronisation may be found elsewhere (e.g. Record, 1980; Summers, 1988). In addition, granulation may be achieved by dry methods such as slugging or roller compaction (Summers, 1988). However, dry granulation is less widely used in comparison with wet granulation techniques. Unless otherwise stated in the following discussion and investigations, 'granulation' refers to wet granulation and 'granule' refers to wet granulated material.

The full process of wet granulation by wet massing and screening may be divided into several processing stages (Sheth et al, 1980; Schwartz, 1988):

a) deagglomeration by milling or sieving of the starting materials,

b) preliminary blending of some or all of the dry ingredients,

c) preparation of the binder solution which is commonly aqueous but which may be alcoholic,

d) wet massing of the powders with the liquid,

e) wet screening,

f) drying,

g) dry screening,

h) final mixing of any remaining dry powder ingredients such as lubricants and disintegrants before compression into a tablet.

During wet massing the powder bed is agitated to facilitate distribution of the granulation fluid. Agitation also results in collision of particles which promotes agglomerate growth. Newitt & Conway-Jones (1958) and Kristensen & Schaefer (1987) have described the mechanical action of the granulator in terms of its influence on the contracting forces exerted by the granulation fluid which cause granule densification and binding. Newitt & Conway-Jones (1958) have defined three stages as the fluid progressively fills the spaces between neighbouring particles. The states of particle agglomeration are distinguished by the type of liquid bond separating the particles, and in order of increasing liquid saturation are known as the pendular, funicular, and capillary states, the latter achieved when all the pore spaces within the granules are filled (Newitt & Conway-Jones, 1958). The cohesive forces between particles and the tensile

strength of the interparticulate bonds also increases as the amount of liquid is increased up to the capillary stage (Newitt & Conway-Jones, 1958). An increase in the amount of added fluid beyond the capillary stage leads to the droplet stage. In this stage all the particle surfaces are surrounded by a continuous water film with concomitant loss of capillary forces and wet mass cohesion so that only surface tension forces hold the drop together. Further, the effect of the proportion of binder fluid on wet mass cohesion may be influenced by the combined effects of binder solution viscosity and surface tension, and by adsorption of the solution binder onto granulated particles (Parker et al, 1990 and 1991).

Granule drying methods are discussed in section 1.2 below. During the drying stage most of the liquid bridges formed between particles during the granulation stage are removed. If particle agglomeration is to be retained in the dry state, liquid bridging forces must be replaced by adequate solid state bonding. The latter is usually achieved by one or more of the following bonding agencies: crystallisation of dissolved materials, deposition of hardening binders, localised particle fusion by "cold" welding, and mechanical interlocking of particles (Sherrington & Oliver, 1981). In addition, electrostatic forces or hydrogen bonding may promote solid state granule integrity. The tensile strength of the granules produced is dependent on the magnitude and nature of the cohesive forces, the bonding surface area within individual particles, the particle size distribution, and the particle surface area (Sherrington & Oliver, 1981).

The performance related characteristics of the final granules may be influenced by the complex interaction of formulation and process variables (Record, 1980; Kristensen & Schaefer, 1987). Granule properties may be affected by the amount of granulation fluid (Kristensen et al, 1984; Chowhan & Amaro, 1988, Staniforth et al, 1988) with the optimal amount of added fluid generally considered to correspond to the amount required to achieve conditions just below the capillary state, that is at maximum strength of the wet agglomerates without addition of excess water which would require higher energy input during drying (Schildcrout, 1984; Kristensen & Schaefer, 1987; Schwartz, 1988). Furthermore, wet massing process conditions including the amount of fluid added but also the mixing intensity during granulation and granulation time have been reported to affect the particle size distribution (Holm et al, 1983 and 1984) and intragranular porosity (Kristensen et al, 1984; Hunter & Ganderton, 1973) of the granules

produced. Results presented by Rue et al (1980) and Seager et al (1982) also indicate that the compactibility of granules prepared from similar formulae may be influenced by process differences, with granule compactibility being proportional to the concentration of the binder present at granule surfaces. The surface tension of the binder solution has also been found to affect dried granule bulk density and the strength and friability of tablets produced (Wells & Walker, 1983). In general the flow characteristics of the formulation are improved as a result of a granulation due to an increase in particle size and a reduction in surface irregularity (Summers, 1988).

Wet granulation in general suffers from the disadvantage of involving several processing stages and is therefore a potentially costly technique in terms of personnel, equipment, space, time and energy. The addition of water may also adversely affect the stability of the active (Sheth et al, 1980). Certain types of granulating equipment, some of which are discussed in section 1.2 below, allow two or more of the discrete processing stages to be combined thereby offering several production - related benefits.

A less commonly used variant of processing wet massed powders prior to tableting is the formation of pellets by the process of extrusion which may then be spheronised (Conine & Hadley, 1970; Reynolds, 1970). This involves preparation of a wet mass containing greater amounts of water than would be used in formulation of conventional wet granules. The dried pellets or spheres may be compressed into tablets, or filled into hard gelatin capsules.

1.1.2.2 Direct compression

Direct compression is the simplest method by which tablets may be manufactured. The technique involves two processing stages: firstly, the active principle is blended with the appropriate excipients and secondly, this powder blend is compacted to produce the finished tablet. The potential advantages of use of direct compression for tablet production have been discussed elsewhere (Mendell, 1972a; Khan & Rhodes, 1973; Armstrong, 1988). In addition to process simplicity and economy, direct compression offers potentially greater chemical stability of the drug. However, the direct compression technique generally requires high performance characteristics from individual components of the formulation since the properties of the drug-excipient blend cannot be easily altered or enhanced by process manipulation. For this reason, tablet manufacture

by the direct compression technique is potentially more problematic than compaction following granulation (Staniforth & McClusky, 1982; Armstrong, 1986). Therefore, despite its relative complexity and other disadvantages, wet granulation remains an important tablet production technique.

1.1.3 Factors influencing formulation compactibility

Tableting involves dry compaction of powders or granules to achieve consolidation by particle rearrangement and deformation or fracture. The purpose of compaction is to bring particle surfaces into close proximity and to enhance intermolecular or other forces, thereby enabling interparticulate bonding (Karehill et al, 1990). The mechanical properties of the resulting compact are dependent on both the intra- and interparticulate bond strength, and on the area of interparticle bonding resulting from powder compaction and decompression (Karehill et al, 1990). Compressibility as defined by Leuenberger (1982) is taken to be the ability of a material to reduce in volume, whereas the term compactibility is used to describe the irreversible reduction in volume which occurs when a material is formed into a mechanically robust compact. Compactibility may be affected by both the physico-chemical characteristics of the material under consolidation as well as the tableting conditions. Krycer et al (1982a) showed that powders exhibiting high compactibility had a high particle friability and porosity. Important formulation characteristics also include the ability of particles to bond following deformation (Rue et al, 1980), particle roughness and shape (Alderbourn & Nyström, 1982a; Wong et al, 1988; Karehill et al, 1990), size and size distribution (Alderbourn & Nyström, 1982b; McKenna & McCafferty, 1982; Ragnersson & Sjogren, 1985; discussed further in section 5.3.2), moisture content (Malamataris et al, 1991; discussed further in section 1.5.4.5), and the amount of elastic recovery occurring during decompression (Hiestand et al, 1977; Rue et al, 1980). Compaction variables which may have a substantial effect on compactibility include load applied, and for viscoelastic and plastically deforming materials the rate of compaction and duration of applied compressive force (David & Augsberger, 1977; Armstrong & Blundell, 1986).

1.1.4 Assessment of powder compaction behaviour

Various techniques have been used to compare and assess the compaction characteristics of powders and granulations used to prepare pharmaceutical tablets, some of which have been discussed by Jones (1981) and Krycer et al

(1982b). Profiles in which some parameter related to tablet mechanical properties is plotted against compaction force or pressure are widely used to assess compactibility. Although such comparisons do not provide information on the fundamental mechanisms involved during compaction of materials (York et al, 1990), such profiles provide a useful method for comparing the compactibility of materials related to their end use providing the data is obtained under compaction conditions relevant to those occurring in real tableting situations (Jones, 1981). Although crushing force (Shotton & Ganderton, 1960) is perhaps the most frequently used parameter to describe the mechanical characteristics of tablets formed, it has been suggested that tablet tensile strength values are more meaningful since they are less dependent on tablet dimensions (Newton et al, 1971). Tensile strength, however, does not accurately reflect the work that can be done on the tablet before failure. This property, which is known as tablet toughness, may be evaluated from corrected work of failure measurements (Rees & Rue, 1977 and 1978a).

1.2 Drying

As part of the processes involved in carrying out wet granulation, a drying stage is required to remove the added liquid. In some wet granulation processing equipment it is possible to combine the wet massing / agglomeration and drying processes in one stage. In addition, an earlier drying stage may have been carried out during the manufacture of individual tablet excipients. For example, the production of MCC involves spray drying of cellulose microcrystals (section 1.5.2). In most cases the liquid to be removed during drying is water.

Drying can be performed using one or a combination of drying techniques. Selection of a suitable drying process for a particular product involves consideration of factors such as the physical form, toxicity, and chemical stability of the feed material as well as economic aspects. In addition, the drying technique may influence the physical characteristics of the final product. A brief discussion of the principles of drying and of drying and agglomeration/drying techniques is presented below. Although relatively little information is available, where possible the comparative effects of various drying techniques on the physical structure of cellulose based materials and of pharmaceutical tablet excipients, including their effect on excipient compaction properties, are discussed below. Non-thermal

dewatering of cellulosic materials by solvent exchange is discussed separately in section 7.2.

1.2.1 Energy and mass transfer during drying

In order to dry a solid, two processes must take place: 1) energy transfer to heat the wet product, and 2) removal of water vapour away from it. Heat energy is transferred to the surface of the material by one or more of the following mechanisms: convection, conduction, or radiation. Energy for drying can also be supplied using electromagnetic radiation in the radio or microwave frequency regions; such drying techniques are termed dielectric methods and are discussed further below.

During non-dielectric thermal drying, moisture removal occurs initially from the product surface. As drying is continued, evaporated surface moisture is replaced by moisture transferred from the interior. Moisture migration can occur by a number of processes including liquid flow by capillary action and diffusion (Stuchly & Stuchly, 1983; Menon & Mujumdar, 1987). During drying of wet granules moisture removal results in an increase in the curvature of the water menisci in the interparticulate spaces (Newitt & Conway-Jones, 1958). As drying proceeds, for spherical particles bound by pendular bonds, the cohesion between particles in wet granules has been shown to increase (Newitt & Conway-Jones, 1958). In addition to product shrinking, case hardening may occur (Stuchly & Stuchly, 1983; Menon & Mujumdar, 1987). In the case of drying of cellulose, it has been suggested that the surface tension of the menisci of evaporating moisture leads to increased hydrogen bonding within the product, and this is discussed further in sections 1.4.1.3 and 1.4.2 (Higgins & McKenzie, 1963; Corte,1980; Robinson, 1980) .

Once transferred to the air-surface interface, moisture from the interior is available for evaporation. The critical moisture content is reached when the surface film cannot be replenished at the same rate as evaporation of surface moisture, resulting in the appearance of dry spots on the product surface. On further drying the surface film may be completely destroyed and evaporation of the moisture from the deeper parts of the material occurs by diffusion from air-surface interfaces within the product when any adsorbed or bound moisture may be removed.

In contrast, providing the material contains a suitably receptive (dielectric) component, dielectric heating is volumetric and independent of surface heat transfer, and moisture removal. Further, unlike thermal drying, dielectric drying is not necessarily initiated by evaporation of surface moisture (Stuchly & Stuchly, 1983; Schiffmann, 1987). During dielectric drying, conditions may be such that surface cooling by radiation and latent heat of evaporation results in a higher temperature in the product interior than at the surface. Vapour may thus be generated within the material at a rate exceeding surface evaporation, and if the material is unable to accommodate the resulting increase in internal pressure or volume, the material may "explode" (Schiffmann, 1987).

1.2.2 Drying techniques

1.2.2.1 Non-dielectric drying methods

Non-dielectric methods include tray drying, vacuum drying, fluidised bed granulation / drying, spray granulation / drying and freeze drying are relatively well known and have been described elsewhere (e.g. Strumillo & Kudra, 1986; Mujumdar, 1987). Spray drying / granulation of pharmaceuticals has been discussed further by Newton (1966). Only aspects relevant to the effect of the aforementioned drying techniques on product characteristics are discussed immediately below.

The final product characteristics for a formulations based on lactose and starch have been found to vary with the fluidised granulation/drying conditions employed (Davies & Gloor, 1971; Aulton & Banks, 1978). In general, however, granulation by the fluidised bed agglomeration/drying technique was reported to produce spherical granules with a lower bulk density and strength in comparison with granules prepared and dried by wet massing and tray drying for formulations principally consisting of either soluble or insoluble components (Veillard et al, 1982). The latter effect was suggested to be a result of the low amount of mechanical energy supplied to the wet mass during densification in fluidised beds (Veillard et al, 1982). Further, Veillard et al (1982) reported that fluidised bed granules exhibited inferior compactibility in comparison with conventional wet massed granules, with tablet strength being inversely proportional to granule porosity. This is in contrast to the findings of Seager at al (1982) who reported that fluidised bed dried paracetamol granules exhibited slightly superior

compactibility over conventional wet massed and dried paracetamol granules despite the high porosity of the former granule type. The latter effect was attributed to an increase in the amount of gelatin binder at the granule surface in the former which resulted in incresed intergranule bonding following compaction (Seager et al, 1982).

Considering spray drying, Masters (1979) suggested that dryer design and operating conditions may have a pronounced effect on the characteristics of the dried product such as particle size, bulk density and particle friability. Spray drying of a variety of solutions and suspensions containing dissolved solids at various temperatures has been discussed by Duffie & Marshall (1953) and Charlesworth & Marshall (1960). In many cases the final particles were observed to be hollow and nearly spherical with a smooth outer surface. However, the discussions were not applicable to spray drying of suspensions in the absence of dissolved solids such as cellulose microcrystals since the latter are unlikely to have strong film forming tendencies. Raff et al (1961) described the preparation of spray dried granules composed principally of calcium sulphate and lactose. The resulting granules exhibited increased bulk density and improved compactibility in comparison with conventional wet granulated material. The effect of spray drying formulations including paracetamol, MCC and gelatin on granule structure and tableting properties has been reported (Rue et al, 1980; Seager et al, 1982). Spray drying yielded granules with a surface shell of binder. This was in contrast to wet massing which resulted in a matrix of binder within the granules. On compression spray dried granules were found to yield stronger and tougher tablets than wet massed granules. The improved compactibility resulting from spray drying was attributed to concentration of binder at the granule surface where it was most available to form intergranular bonds (Rue et al, 1980; Seager et al, 1982).

Considering spray drying of excipients, it has been reported, but without the presentation of experimental results, that spray drying of cellulose microcrystals results in the production of a material with superior compaction properties in comparison with the tray dried product (Battista & Smith, 1962). This is discussed further in section 1.5.3. Gunsel & Lachman (1963) reported that spray dried lactose exhibited improved compactibility in comparison with lactose dried by a conventional technique. Further, the yield pressure of spray dried alpha lactose monohydrate has been reported to be generally lower than for crystalline

lactose (Fell & Newton, 1971).

During freeze drying, the ice structure confers rigidity on the frozen material. Further, since moisture removal occurs by sublimation, under correctly controlled conditions freeze drying may allow the non-shrunken structure to be maintained yielding a high porosity product (King, 1971; Mellor, 1978; Karel & Flink, 1983). However, it is often difficult to avoid the presence of some non-frozen moisture during the process, and product shrinkage has been found to be proportional to the percentage of unfrozen water after freezing (King, 1971).

1.2.2.2 Dielectric drying

Radio frequency and microwave drying both involve generation of heat within dielectric materials by subjecting the wet material to electromagnetic radiation. Dielectric materials are those which contain dipolar ions or molecules capable of being polarized by an electrical field. Electromagnetic waves consist of electric and magnetic components which, during passage through a medium, rapidly oscillate from zero to a maximum in one direction and from zero to a maximum in the opposite direction. When absorbed by a dielectric material, the dipolar ions are accelerated in the direction of the applied field and existing or induced dipoles attempt to align themselves with the field. Since the applied electrical field is rapidly reversing, the ions and dipolar molecules are set into oscillation as they attempt to follow the changing field. The induced molecular motion results in collisions with neighbouring atoms / ions / molecules, and the friction created in turn causes an increase in temperature of the material. At microwave frequencies (400 - 5,000 MHz) dipoles are the major contributor to the heating mechanisms, whereas at the lower radio frequencies (1 - 200 MHz), ionic conductivity assumes greater importance (Jones, 1989). Thus, pure water, which consists of dipolar molecules, generates heat in the presence of microwaves, but for radio frequency heating, ionic species must also be present.

The actual frequencies which may be employed for drying are restricted by international agreement to avoid interference with broadcasting and telecommunications. The principal permitted frequencies are 27.12 and 13.65 MHz (radio frequencies) and 915 and 2,450 MHz (microwave) (British National Committee for Electroheat, 1983). The dielectric constant provides a measure of the insulating capacity or "polarisability" of a material. The loss factor is the

product of the dielectric constant and loss tangent of the material, the latter being a measure of the "viscosity" of the material to the movement of molecules. The loss factors for water with and without ions, paper and timber at radio and microwave frequencies are given in table 1.1 (British National Committee for Electroheat, 1983).

Table 1.1. Dielectric loss factors at radio and microwave frequencies (data from the British National Committee for Electroheat, 1983).

Material	Loss factor	
	at 10 MHz (RF)	at 3,000 MHz (microwave)
Paper containing 10% moisture	0.4	0.4
Wood (yellow birch)	0.1	0.07
Water (pure)	0.36	12.0
Water containing 0.1 molar NaCl	100.0	18.0

When a water-wet material such as cellulose - containing timber which, in the dry or near-dry state, has a low loss factor is subjected to microwave drying, relatively large amounts of heat are generated within the free moisture component of the material compared with that within the substrate. In the case of radio frequency drying, generation of heat is largely dependant on the presence of ions in solution. Since heat generation develops within the water phase rather than the timber, the energy for drying is concentrated where it is most required, that is within the excess moisture. If correctly controlled, dielectric methods of drying can give rise to selective heating, resulting in a moisture levelling effect (Jones, 1986; Stuchly & Stuchly, 1986; Schiffmann, 1987). In conventional drying moisture leaves the outer surfaces in advance of the inner material. Therefore, moisture gradients occur and drying stresses may result. Theoretically, during dielectric drying, moisture is encouraged to leave the centre thickness much more quickly and uniformly, and stresses are therefore less apparent. In practice however, the centre of the material is often observed to be at a higher temperature than the surface. This phenomenon is due to surface cooling as a result of

radiation losses (Schiffmann, 1987). Thus, under certain conditions evaporation of internal moisture may occur at a rate exceeding that of surface moisture resulting in swelling of the product. If the material is unable to accommodate the resulting increase in internal pressure, the product may be stressed and may even "explode" (Schiffmann, 1987). For example, during radio frequency drying of timber rupture of cell walls may occur with consequent deterioration in wood quality (Timber Research and Development Association, 1969). A more complete discussion of the theory of radio frequency and microwave drying with particular reference to drying of cellulose - containing paper and board has been presented by Jones (1986).

Although dielectric drying techniques have been established in the food industry and elsewhere for several years, commercial drying equipment for pharmaceutical granules using microwaves has become available only relatively recently. The development and use of a microwave-vacuum mixer/granulator/ drying system for the pharmaceutical industry has been described by Gillet (1982), Doyle & Cliff (1987), and Smet (1989). Application of reduced pressures in addition to supply of microwave energy results in increased evaporation rates at reduced bed temperatures, the vacuum pump also providing a means for removal of evaporated moisture from the system (Smet, 1989). Condensation may also be reduced by heating the walls of the drying vessel. Energy emission during microwave drying is controlled by the voltage applied to the magnetrons. Thus, once set by the operator, the microwave output will continue at the same level until an external instruction is received. The latter may be given manually or by an automatic feed-back system and can be altered in accordance with for example the product temperature or the E-field reflected from the material (Doyle & Cliff, 1987; Smet, 1989). The E-field is the electric component of the electromagnetic wave. Not all of the transmitted energy is absorbed by the material and as the loss factor of the material decreases (such as a result of drying), the reflected free energy increases and can be measured by an E-field probe (Doyle & Cliff, 1987).

It has been reported, but without presentation of data, that microwave - vacuum dried granules prepared from an unspecified formulation "tableted well" and formed tablets with comparable properties to those prepared from tray dried granules (Gillet, 1982). The effects of microwave drying without vacuum on paper quality have been compared with conventional drying techniques (Kumar et al, 1990). Microwave drying was found to yield paper of similar quality to that

obtained by conventional drying techniques. In particular, it was not found to affect the strength, density, or optical properties which suggested that the technique did not reduce the compacting effect of surface tension effects caused by water removal.

Until now, radio frequency drying has not been applied to drying of pharmaceutical granules although the technique is widely employed in the food industry for the post-baking of biscuits, and by the textile and paper industries (Jones, 1987 and 1989). Radio frequency drying involves placing the material to be dried between two electrodes where it acts as the dielectric component of a capacitor. The simplest electrode configuration consists of two flat metal plates between which the material to be heated is placed. Such a system is termed a "through field" system. The electrodes are connected to a radio frequency generator via flexible copper leads or a coupling coil. Supply of a high frequency voltage to the electrodes results in the generation of radio frequency electromagnetic radiation within the product. The development of maximum power inside the feed material is achieved by tuning of the circuit, for example by adjusting the distance between the electrodes, to obtain a frequency just above the generator frequency. As drying proceeds, the voltage across the product must be increased if energy transfer is to be maintained. Moisture condensation is prevented by the use of a flow of warm air. The use of reduced pressures with radio frequency drying is not advised since the combination carries the risk of electrical discharge (Jones, 1989).

Aside from differences in the type of generator and the design of the drier, perhaps the principle practical difference between microwave and radio frequency drying is that in the latter the product forms part of the electrical circuit from which the drying radiation is produced, whereas in the former it does not. Thus, in theory radio frequency drying can be designed to be truly self-regulating with a reduction in the moisture content or in the quantity of the material being dried resulting in a decrease in the power transferred from the radio-frequency generator (Jones, 1989). Radio frequency drying also has advantages over microwave-vacuum drying with respect to reduced equipment costs. Radio frequency drying has been found to result in improved moisture profile correction in paper than may be achieved with microwave drying (Jones, 1986). However, microwave heating offers the potential for higher heating rates in comparison with radio-frequency heating (Stuchly & Stuchly, 1986).

1.3. Cellulose

Cellulose is found in abundance throughout the plant kingdom and is the major structural component of plant cell walls. Detailed discussions regarding the structure of cellulose, including aspects referred to below on which opinions are divided, may be found elsewhere (e.g. Howsmon & Sisson, 1954; Marchessault & Sundararajan, 1983; Haigler, 1985; Preston, 1986; Atalla, 1987). Brief summaries of the structure of cellulose and its various polymorphs, together with properties relevant to discussions related to subsequent investigations in the present study are presented below.

1.3.1 The structure and characterisation of cellulose and its polymorphs

1.3.1.1 Chemical structure

Cellulose is a naturally occurring polysaccharide composed of D-anhydroglucopyranose units linked through 1-4-ß-glycosidic bonds (figure 1.1). The degree of polymerisation of cellulose in wood pulp is of the order of 600 to 1,000 although this varies according to plant source, cellular site, and extent of degradation during isolation (Kraemer, 1938).

1.3.1.2 Generalised physical structure

The ß-1,4 linkage between each saccharide component molecule results in cellulose exhibiting a ribbon-like structure. The hydroxyl group stretching vibration in the infra red spectrum of cellulose occurs at 3300 cm^{-1} whereas for unbonded hydroxyl groups the frequency of the hydroxyl group stretching vibration is approximately 3600 cm^{-1}. This has been interpreted as an evidence that virtually all the hydroxyl groups in cellulose are involved in bonding (Marrinan & Mann, 1954). It is generally considered that the molecular structure of cellulose includes intramolecular O(5)---O(3') and O(2)---O(6') hydrogen bonds which render cellulose molecules rigid (figure 1.2). Adjacent cellulose molecules are also bonded through O(6)---O(3) hydrogen bonds which results in a sheet - like structure similar to that shown in figure 1.2 (Blackwell et al, 1977; Sarko, 1976; Marchessault & Sundararajan, 1983). Hydrogen bonding is discussed further in section 1.3.2 below.

Cellulose 'sheets' are in turn stacked one upon the other as shown in figure 1.3, successive sheets assumed to be held in the stack by van der Waals

Figure 1.1 The cellulose molecule (n ≈ 1,000 to 15,000)

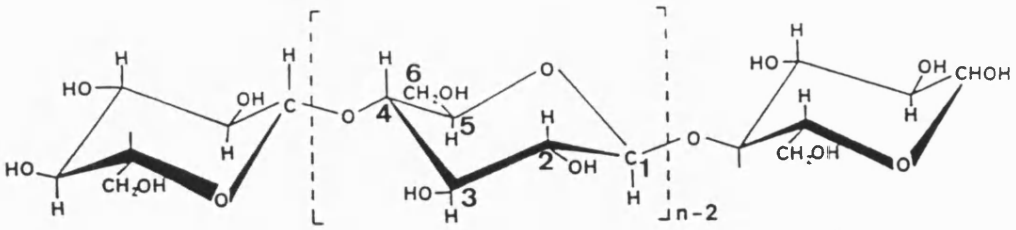


Figure 1.2 Schematic diagram indicating the intramolecular hydrogen bonds which are responsible for the rigidity of cellulose molecules, and intermolecular hydrogen bonds which hold adjacent chains together as 'sheets'.

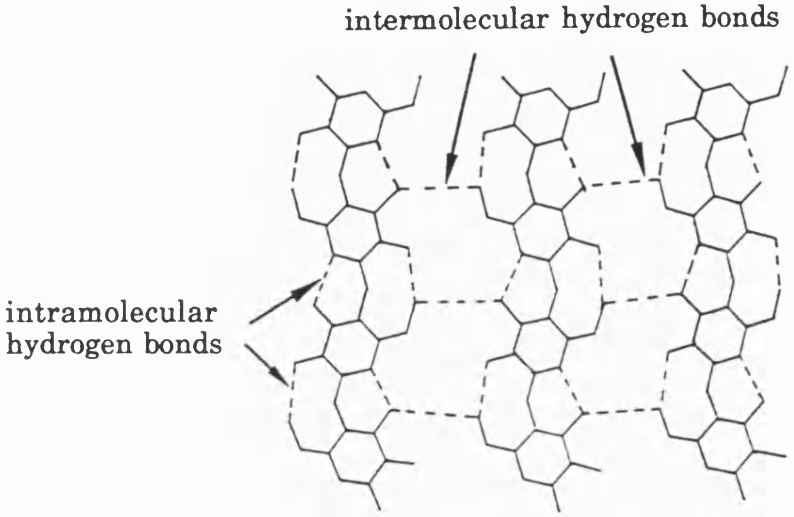
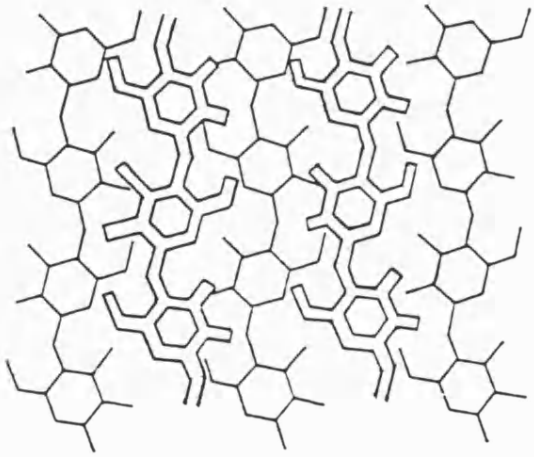


Figure 1.3 Schematic diagram showing the stacking arrangement of cellulose 'sheets'. Attraction between successive sheets results from Van der Waals forces.



forces (Marchessault & Sundararajan 1983; Young, 1986). In native cellulose, cellulose chains in adjacent sheets are generally considered to be arranged in parallel (Blackwell, 1977; Sarko, 1976 and 1987; Atalla, 1983 and 1987). Chain folding is considered unlikely for several reasons; native cellulose chains are thought to be arranged in parallel within elementary fibrils, periodicities along the fibrillar length do not always occur, and because of the small dimensions of the elementary fibrils (Bourret, 1972; Marchessault & Sundararajan, 1983).

In its native form, cellulose chains are aggregated into fibrous structures termed elementary fibrils approximately 3.5 by 3.5 nm in cross section. These elementary fibrils are aggregated into microfibrils, the dimensions of which vary with the biological source and the stage of plant development (Haigler, 1985). The chain axis coincides with the long crystallite axis which coincides with the fibrillar axis (Marchessault & Sundararajan, 1983).

1.3.1.3 Cellulose I and II

Chemical treatments and processing of cellulose generates a variety of polymorphic forms. The naturally occurring crystalline form of cellulose (native cellulose) is termed cellulose I. Cellulose I may be converted into cellulose II by one of two general methods:- a) chemical transformation using regeneration methods such as the cuprammonium or viscose processes in which the cellulose is dissolved and then reprecipitated (Marchessault & Sundararajan, 1983), and b) by swelling treatments involving transformation of cellulose I to II, apparently in the solid state, either as the result of treatment with alkali (mercerisation) followed by washing and drying (Chanzy & Roche, 1976; Sarko, 1986; Marchessault & Sundararajan, 1983), or as the result of milling or intense agitation of cellulose in the presence of water, discussed further in section 11.4.2.5.

Atalla (1983) has suggested that the molecular conformation associated with cellulose I contains a certain amount of strain, with the anhydroglucose units assuming non-equilibrium positions. Further, following swelling, intracrystalline strains are relieved allowing the molecules to become relaxed into the thermodynamically more stable conformation characteristic of cellulose II which persist following removal of the swelling agent and drying (Atalla, 1983).

Cellulose I and II differ from each other with respect to their x-ray diffraction patterns, infra-red, Raman, and solid state ^{13}C NMR spectra (discussed

further in section 11.4.1). The differences in their physical characteristics suggests that polymorphs I and II differ with respect to chain packing mode and intermolecular interaction. Blackwell et al (1977) has suggested that cellulose II is more strongly interbonded and more densely packed in comparison with cellulose I molecules. Furthermore, ^{13}C NMR (Atalla, 1980) and Raman (Atalla, 1983) spectra have been interpreted as indicating the presence of two types of glycosidic linkages along the cellulose chain in both cellulose I and II with adjacent glycosidic linkages along the chain being nonequivalent. Differences between the molecular conformations of cellulose chains in polymorphs I and II may be associated with the locus of the nonequivalence in addition to chain packing mode and intermolecular interaction (Atalla, 1983). Solid state ^{13}C NMR spectroscopy has also been used to provide evidence for the existence of two forms of cellulose I designated Iα and Iβ , the ratio of the two forms varying with the biological source (Vanderhart & Atalla, 1984). The two forms have been suggested to possess similar molecular conformations whilst differing with respect to their hydrogen bonding patterns (Vanderhart & Atalla, 1984).

The transformation of cellulose I to cellulose II is generally irreversible. Thus, it has been argued that cellulose I is thermodynamically metastable and uniquely a product of biosynthesis during which crystallisation and polymerisation occur simultaneously (Haigler, 1985). However, Atalla & Nagel (1974) have reported that cellulose I can be regenerated from its solution in 85% phosphoric acid at 170°C in glycerol suggesting that under carefully controlled conditions the metastable form may be prepared.

1.3.1.4 Cellulose III and IV

In addition to cellulose I and cellulose II, at least two other polymorphic forms of cellulose are generally recognised. Cellulose III may be prepared by treating cellulose I or II with liquid ammonia or with certain amines. Cellulose IV may be prepared by certain heat treatments of cellulose I or II. Further details regarding the preparation of cellulose III and IV may be found elsewhere (e.g. Ellefsen & Tonnesen, 1971; Marchessault & Sundararajan, 1983). Atalla (1976) and Atalla et al (1977) reported that the Raman spectra for cellulose III and IV may be reproduced by linear combination of spectra for cellulose I and II. This was interpreted as evidence that the conformations existing in cellulose I and II

are the only stable conformations (Atalla, 1976; Atalla et al, 1977). Polymorphs I, II, III and IV have, however, been shown to exhibit different X-ray diffraction patterns (Ellefsen & Tonnesen, 1971; Nelson & O'Connor, 1964a), suggesting that celluloses III and IV may exhibit distinct packing modes.

1.3.1.5 The crystalline / 'amorphous' nature of cellulose

Although grossly crystalline, microfibrils of native cellulose may also contain some less ordered material and can therefore be considered to be composed of two distinct morphological regions:-

a) crystalline regions which consist of molecules arranged with a high degree of order as described in section 1.3.1.2 above. These regions are approximately 60 nm in length with widths and thicknesses in the range 5 to 10 nm (Stamm, 1977). Unless swollen by methods discussed in section 1.3.1.3 above, crystalline cellulose is generally unreactive (Stamm, 1977; Marchessault & Sundararajan, 1983; Young, 1986), and has been demonstrated to be unable to adsorb water (Hermans & Weidinger, 1949). This is due to the high degree of packing regularity and lateral bonding between chains within crystalline regions. Crystalline regions may also exist in polymorphic forms of cellulose other than native cellulose.

b) 'amorphous' or 'accessible' regions in which the molecules are less highly bonded and perhaps less well ordered. Amorphous regions may also exist in polymorphic forms of cellulose other than cellulose I. The term amorphous may, however, be misleading since it has been demonstrated that within microfibrils the fraction which is not highly crystalline contains a significant degree of intermolecular bonding and a reasonable degree of order, with the degree of order varying along the microfibrillar length (Stamm, 1977). In contrast to cellulose molecules in crystalline domains, the glycosidic groups of cellulose molecules in amorphous regions are susceptible to hydrolysis, and the hydroxyl groups are accessible for interaction with, for example, water molecules (Valentine, 1958).

Jeffries et al (1968) suggested that the physical state of water molecules may affect the degree of interaction between cellulose and water; for example these workers suggested that the accessibility of liquid water to cotton was only approximately two-thirds that of the accessibility of similar samples to water

vapour. To differentiate between the take-up of water from the vapour phase and from the liquid phase, in the following discussion and studies the former is termed adsorption, the latter absorption. When the exact nature of the mechanism is unclear, the term sorption is used. The adsorption / desorption isotherms for water on cellulosic materials are discussed in section 1.5.1.4. Adsorption of water by cellulose on active sites is accompanied by evolution of heat (Chapter 10). Furthermore, perhaps as a consequence of the lower degree of packing regularity and three-dimensional bonding, the infra-red, Raman, and solid state ^{13}C NMR spectra exhibited by amorphous regions differs to that exhibited by crystalline forms of cellulose, and unlike crystalline regions amorphous cellulose provide a diffuse X-ray diffractogram (section 11.4.1).

A variety of models have been proposed for the crystalline-amorphous structure of different polymorphic forms of cellulose. Those which have gained general acceptance may be classified into one of two groups (Young, 1986; Marchessault & Sundararajan, 1983); 1) a single phase crystalline structure in which the amorphous fraction is considered to occur in the form of periodic dislocations (Bourret et al, 1972; Preston, 1986) and 2) a continuous two-phase structure in which cellulose chains are envisaged as passing through successive well ordered and less well ordered regions (Howsmon & Sisson, 1954). Marchessault & Sundararajan (1983) suggested that native cellulose is best described by the continuous structure theory, and regenerated cellulose by the two-phase theory (figures 4 and 5 in appendix i). A description of the crystalline / amorphous structure for cellulose is further complicated by the presence of intermediate phases between truly amorphous and truly crystalline.

Differences between the physical and chemical characteristics of amorphous and crystalline cellulose, some of which have been discussed above, may be used to evaluate the degree of crystallinity or the degree of accessibility of samples of cellulose. Reviews of such techniques together with their relative advantages and disadvantages have been presented by Tripp (1971) and Wadsworth & Cuculo (1978). According to Wadsworth & Cuculo (1978) the techniques may be divided into a) physical methods such as X-ray diffraction and infra red spectroscopy which generally measure some function of the degree of molecular order within samples, b) chemical swelling methods such as water vapour sorption in which the proportion of the sample available to interact with a

reagent which is capable of disrupting hydrogen bonds is evaluated, and c) non-swelling chemical methods such as nitrogen adsorption in which the availability of the sample to a reagent unable to disrupt hydrogen bonds is measured. In the methods described in point c) immediately above, the amount of physical accessible surfaces rather than the degree of disorder is determined (section 1.5.4.6). Thus, these methods are regarded by most workers as inappropriate for determining degree of crystallinities. The state of order within samples of cellulose may not be divided into distinct crystalline and amorphous parts since a spectrum of order exists with several degrees of intermediate or semicrystalline order. With different techniques, this order may be perceived and therefore quantified differently (Tripp, 1971; Wadsworth & Cuculo, 1978). Determination of the degree of crystallinity or order within cellulosic samples containing mixed crystal lattices is further complicated by differences in the response of different crystalline polymorphs to the characteristic under observation (Nelson & O'Connor, 1964b; Wadsworth & Cuculo, 1978).

1.3.2 Hydrogen bonding

Hydrogen bonding occurs between functional groups in which the hydrogen is attached to oxygen or nitrogen. In the case of cellulose, hydrogen bonding may occur between adjacent hydroxyl groups. In a hydroxyl group, the electron previously associated with the hydrogen atom is involved in forming a covalent bond with the oxygen atom, and is therefore concentrated within the bonding region between the two nuclei. Consequently, away from the covalent bond region the hydrogen nucleus does not have an appreciable electronic cloud, and therefore has a partially positive character. This results in attraction between the hydrogen of one hydroxyl group and the lone pair electrons from an oxygen atom of a neighbouring hydroxyl group. The attraction is known as a hydrogen bond (Sanderson, 1983). Stabilisation of the bond may arise by resonance of the primary valence bond between the two oxygen atoms associated with the hydrogen atom. The formation of a hydrogen bond requires a minimum intermolecular distance of approximately of 2.5 to 3.5 Angstroms (Sanderson, 1983). Hydrogen bonds have a strength of approximately 10 $kJmol^{-1}$, which is less than the energy of typical chemical primary valence bonds (approximately 500 $kJmol^{-1}$), and greater than a typical van der Waals interaction energy (approximately 1 $kJmol^{-1}$) (Caulfield, 1980; Sanderson, 1983).

1.4 'Cellulose' fibres and their bonding and formation into paper

Research in the field of paper chemistry has included studies of the relationship between the physico-chemical and physico-mechanical characteristics of cellulose fibres, and more importantly in relation to the present study how drying from water may affect final fibre properties. In subsequent sections of the present study it is considered that interesting parallels exist between the behaviour and properties of cellulose fibres and those of microcrystalline cellulose. For this reason, selected aspects of cellulose fibre characteristics with respect to papermaking are considered below.

1.4.1 The papermaking process

1.4.1.1 'Cellulose' fibres and wood pulp

Paper is commonly manufactured from pulped wood fibres. Although commonly termed 'cellulose fibres', wood fibres contain other substances in addition to cellulose. Approximately 40% of the dry weight of wood fibres is cellulose in the form of microfibrils (see section 1.3.1.2), the other principle components being hemicellulose and lignin. Hemicellulose is commonly used as a collective name for the mixtures of polysaccharides in plant cell walls which, unlike cellulose, are soluble in dilute acids and which on hydrolysis yield glucose, mannose, galactose, arabinose, and uronic acid (Nikitin, 1966b; Whistler & Richards, 1970). The hemicelluloses present in a cell wall vary widely in their composition and structure. Commonly they are heteropolymers of a lower molecular weight than cellulose and are often branched structures (Nikitin, 1966b; Whistler & Richards, 1970; Emerton, 1980). Lignin is a complex aromatic polymer suggested to be highly cross-linked into a three dimensional structure, the precise structure of which is still unknown (Emerton, 1980; Glasser, 1980).

The structure and composition of wood fibres has been described in detail elsewhere (e.g. Emerton, 1980; McGinnis & Shafizadeh, 1980; Young, 1986). Fibres are composed of a series of concentric layers varying in thickness, fibril orientation and chemical composition. The outer layer or middle lamella is primarily composed of lignin with a smaller component of hemicellulose. The next layer is the thin primary wall layer which like the secondary wall layers consists of cellulose microfibrils embedded in a matrix of hemicellulose and lignin. The thickest of the secondary wall layers, the middle layer, is composed of

concentric lamellae. In the cell wall cellulose, hemicelluloses, and lignins are thought to exist in close association, physically entangled and held by secondary forces such as van der Waals forces and hydrogen bonding (section 1.3.2) with perhaps some interconnecting primary bonds (Whistler & Richards, 1970). Cellulose is the major structural component of cell walls. In the secondary wall, cellulose microfibrils form a helix around the cell with each of the layers or lamellae containing microfibrils arranged in parallel, and the helix formed by successive lamellae varying in pitch and screw orientation (Preston, 1986).

During pulping the fibres are separated from each other either by chemical or mechanical means, or by combinations of the two. Chemical methods are most commonly employed to provide fibres for paper making and involve removal of the lignin with minimal dissolution of hemicelluloses and cellulose (Casey, 1980).

1.4.1.2 Beating

Although processes used to make paper vary with the characteristics required of the final product, in general the pulp is firstly slurried in water and beaten or refined before forming into a wet web and drying. As a result of the intense mechanical action involved, beating results in partial disruption of lateral bonds between lamellae in the fibre walls which increases fibre flexibility and improves the ability of the fibres to absorb water (Higgins & McKenzie, 1963; Robinson, 1980). Absorbed water may contribute to the increased fibre flexibility observed by further separating cellulose microfibrils from one another and plasticising cellulose chains within the amorphous regions (Caulfield & Weatherwax, 1978). Furthermore, by causing fraying of the fibre surface, beating increases the fibre physical surface area (Ingmanson & Andrews, 1959; Higgins & De Yong, 1962; Stone et al, 1968). In addition to affecting the general fibre, as a result of beating some of the hemicellulose content is worked from the interior of the fibre wall to the fibre surface where it may serve as a bonding agent during drying of the wet web (Wardrop, 1962; Eastwood & Clarke, 1978). Beating of the pulp before papermaking thus improves the mechanical properties of the paper sheet produced by its combined effect on the fibre flexibility and the chemical and physical nature of the fibre surfaces (Higgins & McKenzie, 1963; Stone et al, 1968; Robinson, 1980). However, beating also reduces the strength of individual fibres. Thus, maximum paper strength is attained with an optimal rather than maximal amount of beating (van den Akker, 1952; Higgins & De Yong, 1962).

Furthermore, with a high amount of beating the proportion of fibre fragments (fines) in the wet pulp may be increased which tends to reduce the paper drainage properties and results in inferior paper formation characteristics (Szwarcsztajin & Przybysz, 1978; Robinson, 1980).

1.4.1.3 Surface tension effects and fibre bonding during drying

The mechanisms by which fibre bonding occurs during drying and drainage of wet webs have been discussed by Corte (1980) and Robinson (1980). In the wet web, water is present both between and inside fibres, the amount of internal water increased by beating as discussed above. During drying, surface tension effects result in consolidation of the wet sheet as fibres are brought together and individual fibres collapse (Page, 1967; Stone et al, 1968). As intra- and interfibre water disappears, true intra- and interfibre bonding commences, probably by hydrogen bonding which immobilises the contracted structure.

Since hydrogen bonding requires hydroxyl groups to be in close proximity (section 1.3.2), fibre deformability, which is affected by beating and the degree of swelling as discussed above, and surface tension are considered important factors in determining the degree of bonding in the final sheet (Corte, 1980; Robinson, 1980). Processes which reduce the surface tension during drying have been shown to reduce paper strength. For example paper dried by freeze drying has been reported to have high bulk and low strength in comparison with air dried paper (van den Akker, 1952). The reduction in paper strength caused by freeze drying has been partly attributed to the reduction in surface tension and therefore interfibre bonding during drying, and partly to a reduction in individual fibre strength since ice formation causes fibre damage (Higgins & McKenzie, 1963; van den Akker, 1952). Paper strength may also be reduced by addition of a surfactant to the pulp before drying (van den Akker et al, 1958). Surfactants may reduce paper strength not only by reducing surface tension during drying but also by adsorption onto the fibre surfaces which masks the hydroxyl groups and reduces their potential for hydrogen bonding (Higgins & McKenzie, 1963; Robinson, 1980). In addition, replacement of the water by a liquid with lower polarity before drying and drying the wet sheet from the exchanged liquid is also known to reduce the strength of paper produced, perhaps by suppression of orientation of the hydroxyl groups into the intra- and interfibre spaces as well as by reducing the surface tension during drying (Higgins & McKenzie, 1963; Robinson, 1980).

Fibre drying by solvent exchange is discussed further in section 7.2.

From the infrared spectrum of cellulose, it is apparent that practically all the hydroxyl groups are involved in hydrogen bonding (Marriman & Mann, 1954). Evidence for interfibre hydrogen bonding in paper is less direct since the number of such bonds arising as a result of paper-making is a small fraction of the total number of hydrogen bonds in paper and therefore may be expected to be difficult to detect by spectroscopic techniques (Higgins & De Yong, 1962). Indirect evidence regarding the importance of hydrogen bonding to the strength of paper produced has been discussed by Higgins & McKenzie (1963) and more recently by Corte (1980) and Robinson (1980) and includes the observation that paper disintegrates readily in liquids of high polarity such as water, but less readily in organic liquids. In addition the successive reduction in paper strength following increasing degrees of acetylation of hydroxyl groups on the fibre (Bletzinger, 1943) has been interpreted as providing support for the theory of hydrogen bonding within paper.

It should also be noted that the formation of hydrogen bonding as a result of drying is not confined to the cellulose fraction of fibres, but also to the hemicelluloses. Indeed, the high swelling capacity and relatively high mobility of hemicelluloses together with their relatively high concentration on the fibre outer surface, particularly after beating, has led workers to suggest that their swelling and therefore collapse may provide important contributions to the overall bonding within dried paper sheets, the hemicelluloses functioning as fibre adhesives (Wardrop, 1962; Nikitin, 1966b; Eastwood & Clarke, 1978).

1.4.2 'Hornification' and loss in bonding capacity of cellulosic fibres

Predrying of cellulose pulp prior to paper manufacture is often necessary to facilitate storage and transportation. In addition, paper is sometimes manufactured from dried paper offcuts, or from waste (used) paper rather than virgin wood pulp. Paper made from secondary (predried) fibres however has inferior strength in comparison to paper manufactured from primary (never been dried) fibres from a similar source (Higgins & McKenzie, 1963; Eastwood & Clarke, 1978; Szwarcsztajin & Przybysz, 1978; Klungness & Caulfield, 1982).

The phenomenon of reduced bonding capacity following drying and rewetting has been termed hornification since the secondary fibres exhibit reduced

swelling capacity in comparison with primary fibres (Howarth, 1978; Szwarcsztajin & Przybysz, 1978; Klungness & Caulfield, 1982). The mechanism by which fibres hornify has been discussed by several workers (e.g. Higgins & McKenzie, 1963; Howarth, 1978; Robinson, 1980; Klungness & Caulfield, 1982). There is general agreement that at least part of the loss in paper strength following pulp predrying is due to the formation of intra- and interfibre hydrogen bonds during the preliminary drying stage, some of which are irreversible on rewetting. The irreversibility of the hydrogen bonds has been attributed to the high degree of lateral association which reduces the accessibility of the fibres to water in a manner similar to that rendering crystalline regions inaccessible to water as discussed in section 1.3.1.5 (Higgins & McKenzie, 1963). Secondary fibres thus exhibit reduced flexibility and a lower interfibre surface area during formation and drying of the wet web which results in a lower overall paper strength. The reduction in bonding ability of fibres following preliminary drying has also been attributed to an alteration in the surface condition of the fibres, perhaps by hornification of or a reduction in the hemicellulose fraction within pulps (Giertz, 1962; Eastwood & Clarke, 1978). Furthermore, it has been suggested that the reduction in paper strength following an intermediate drying stage may be attributed to fibre damage and shortening during repulping stage (Howarth, 1978). However, results presented by Eastwood & Clarke (1978) indicates that recycling causes little, if any, reduction in individual fibre strength which suggests that the loss in paper strength from secondary fibres is primarily due to a reduction in bonding ability.

1.4.3 Techniques for improving fibre bonding capacity and for reducing hornification

The strength of paper produced from pulps containing secondary fibres may be improved by addition of never dried fibres (Howarth, 1978) or by the addition of substances such as high molecular weight hydrophilic colloids which may act as adhesives in the pulp (Robinson, 1980). Alternatively, the bonding properties of dried and rewetted fibres may be improved by beating the secondary fibre pulp thereby reducing intra- and interfibre bonding (Giertz, 1962; Caulfield & Klungness, 1982), although excessive beating may result in undesirable fibre damage and a reduction in the drainage ability of the wet web as discussed in section 1.4.1.2 above. In addition, it has been reported that performing the initial or secondary pulping in an alkaline medium or in a solution containing high

valence anions improves the ability of secondary fibres to bond during papermaking, perhaps by inhibiting or disrupting hornification involving carboxyl groups in the hemicellulose and lignin fractions of the fibres (Lindstroem & Carlsson, 1982; Young, 1986).

Increasing the amount of beating before the preliminary drying has been found to result in a successive reduction in the strength of paper produced from reslushed pulp presumably because at higher levels of beating the bonding occurring during the preliminary drying stage is increased (Higgins & McKenzie, 1963). Thus, by reducing the amount of beating before the preliminary drying, hornification may be reduced. In addition, increasing the temperature at which the primary pulp is dried from 25 to 125 °C has been reported to result in a greater reduction in swelling ability of pulps (Treiber & Abrahamson, 1972). Giertz (1962) also stated that the degree of hornification resulting from drying of pulps was influenced by the temperature and speed of the drying process used although actual experimental results were not given by the author. It may thus be inferred that with the correct choice of drying conditions hornification may be minimised.

Higgins & McKenzie (1963) have investigated the effects of adding various materials to cellulose pulps prior to drying with the objective of preventing the formation of cellulose - cellulose bonds which are irreversible on rewetting with water. The authors considered mechanisms by which additives may inhibit the formation of irreversible bonds including; a) the addition of surface active agents to reduce fibre collapse during drying, b) addition of water soluble materials capable of bonding with cellulose during drying but which on rewetting of the pulp are released, thereby serving to protect the hydroxyl groups from the formation of bonds which are irreversible on reslushing, c) addition of materials which prevent fibre collapse by acting as bulking agents and d) addition of materials which inhibit hydrogen bond formation. The effectiveness of the additives were assessed by comparison between the loss in paper strength following intermediate air drying in the presence and absence of the additive. Partial recovery of bonding capabilities of never-dried fibres was achieved by intermediate drying in the presence of some additives, discussed further in Chapter 12.

In addition, hornification may be reduced by partial acetylation (3-4%) of hydroxyl groups on fibres before the preliminary drying stage (Ehrnrooth et al,

1978). In the aforementioned study it was suggested that steric hindrance of the acetyl groups inhibits the formation of irreversible hydrogen bonds between hydroxyl groups located near the acetylated hydroxyl groups.

1.4.4. Determination of the degree of hornification

As discussed in section 1.4.1.3 above, any increase in hydrogen bonding resulting from drying is unlikely to be directly quantifiable by spectroscopic techniques due to the high degree of hydrogen bonding already present in unhornified fibres (Higgins & De Yong, 1962). Thus, techniques for measuring the degree of hornification following drying have been based on measurement of an alteration in one or more fibre properties which are changed as a result of drying.

Since fibres are made into paper sheets in the wetted state, methods for investigating hornification have been centred around measurements in the wetted state. It has been suggested that the rate at which cellulose is enzymatically degraded into glucose by cellulases may indicate the degree of fibre bonding and thus hornification. However, differences in degradation rate observed between pulps may also be attributed wholly or partially to differences in the hemicellulose content or size distribution of disintegrated paper (Howarth, 1978). Klungness & Caulfield (1982) used a method described by Page (1967) to compare the degree of collapse of fibres in the wetted state whereby collapse of the fibre lumen was observed microscopically. Stone & Scallen (1968) have suggested the use of a solute exclusion technique by which fibre porosity and thus degree of interfibre bonding following rewetting may be measured. This technique is based on the determination of the non-solvent water in wet slurries of the samples. The water bound to the cellulose fibres cannot partake in dissolution of the dissolved substance in the surrounding solution and may thus be used to estimate the volume of internal pores below a certain size, which is determined by the hydrodynamic size of the solute molecules used in the investigation.

Hopner et al (1955) have described a method by which the swelling power of cellulosics may be compared by determining their water retention value following swelling and centrifuging under standard conditions. The technique involves swelling the samples in water followed by centrifugation using horizontally swinging buckets in specially constructed containers which allow water forced out of the sample to be removed. It was suggested that information

regarding the water swelling capacity of samples could be obtained by determining the amount of water retained by samples following centrifuging under standardised conditions for a specified time. Water retention values have been found to correlate with the strength of paper produced following repeated recycling (Szwarcsztajin & Przybysz, 1978), although the nature of the water retained was incompletely defined.

1.5 Microcrystalline cellulose

Microcrystalline cellulose (MCC) is prepared by physically modifying cellulose. Like unmodified cellulose, MCC is chemically stable in air and stable at humidities and temperatures normally encountered during its usage. It is also generally regarded as safe for human consumption, non-digestible, physiologically inert, colourless and tasteless, and has been reported to be chemically compatible with a wide variety of drugs and excipients (The Handbook of Pharmaceutical Excipients, 1986). In addition to the above properties, the process used to manufacture MCC from cellulose (described below) provides an excipient with unique and desirable physico-mechanical characteristics which have resulted in MCC becoming widely used as a pharmaceutical tablet excipient in both directly compressed and wet granulated formulations.

1.5.1 Grades and commercial forms

MCC is available in different tableting grades and from various manufacturers. The first available commercial forms of MCC suitable for use in tableting were the Avicel grades (F.M.C. Corp., Philadelphia, U.S.A.). The majority of studies concerned with the properties of MCC refer to Avicel grade PH-101, or to the larger particle size grade, Avicel PH-102. Commercial forms other than Avicel such as the Emcocels (Edward Mendell Co. Inc., Patterson, New York, U.S.A.) and Unimacs (Uniteka Rayon Co., Japan) are probably manufactured by a broadly similar process, although minor variations may occur, perhaps accounting for differences reported elsewhere between the characteristics of various MCCs. Differences between the physico-chemical properties of various grades and commercial forms of MCC, in particular differences between Avicel and Emcocel materials, have been reviewed previously (Chatrath & Staniforth, 1988 and appendix i). More recently, Rowe & Sadeghnejad (1987) and Parker et

al (1988) have reported that various commercial forms of MCC may differ with respect to their wet massing characteristics. Further, Parker (1989) has reported that the X-ray diffractograms and the water adsorption characteristics of Avicel PH-101 differ from that of Unimac MG-100.

1.5.2 General manufacturing method

The manufacturing process for Avicel has been described by Battista & Smith (1962), Battista (1965), and Lamberson & Raynor (1976) and is shown diagrammatically in figure 1.4. The starting material for MCC is high purity cellulose wood pulp. The cellulose is partially hydrolysed, typically using hydrochloric acid, under controlled conditions and with intense agitation. As discussed in section 1.3.1.5, in comparison with 'amorphous' regions, crystalline regions exhibit greater resistance to acid hydrolysis. Consequently, glycosidic bonds in amorphous regions are preferentially hydrolysed with the reaction rate gradually slowing until most of the glucose units therein are removed (Nelson & Tripp, 1953; Battista & Smith, 1962). Hydrolysis is stopped at this stage. The remaining solid fraction largely consists of crystallites released from the original fibres (Nelson & Tripp 1953; Battista & Smith, 1962). Following washing and neutralisation, microcrystals are spray dried to produce a fine MCC powder. It has been suggested that when spray dried, microcrystals reagglomerate in a random manner forming porous particles (Battista & Smith, 1962; Battista, 1965). Without direct experimental evidence, it was also suggested that intermicrocrystal bonding within individual particles arose from hydrogen-bonds formed between adjacent hydroxyl - rich microcrystal surfaces (Battista & Smith, 1962; Battista, 1965; Lamberson & Raynor, 1976).

1.5.3 Effect of drying technique on the characteristics of MCC

Battista & Smith (1962) reported that freeze dried MCC or MCC dried from propanol or methanol exhibited a higher bulk density than spray dried MCC. Further, in the same study drum and oven dried MCC was described as having 'less desirable' physical properties in comparison with spray-dried material (Battista & Smith, 1962), although these properties were not defined. However, possible reasons for such differences were not discussed. In addition, if instead of spray drying the microcrystals were dispersed in water with intense shearing, stable dispersions or gels were reported to be formed which could be dried into

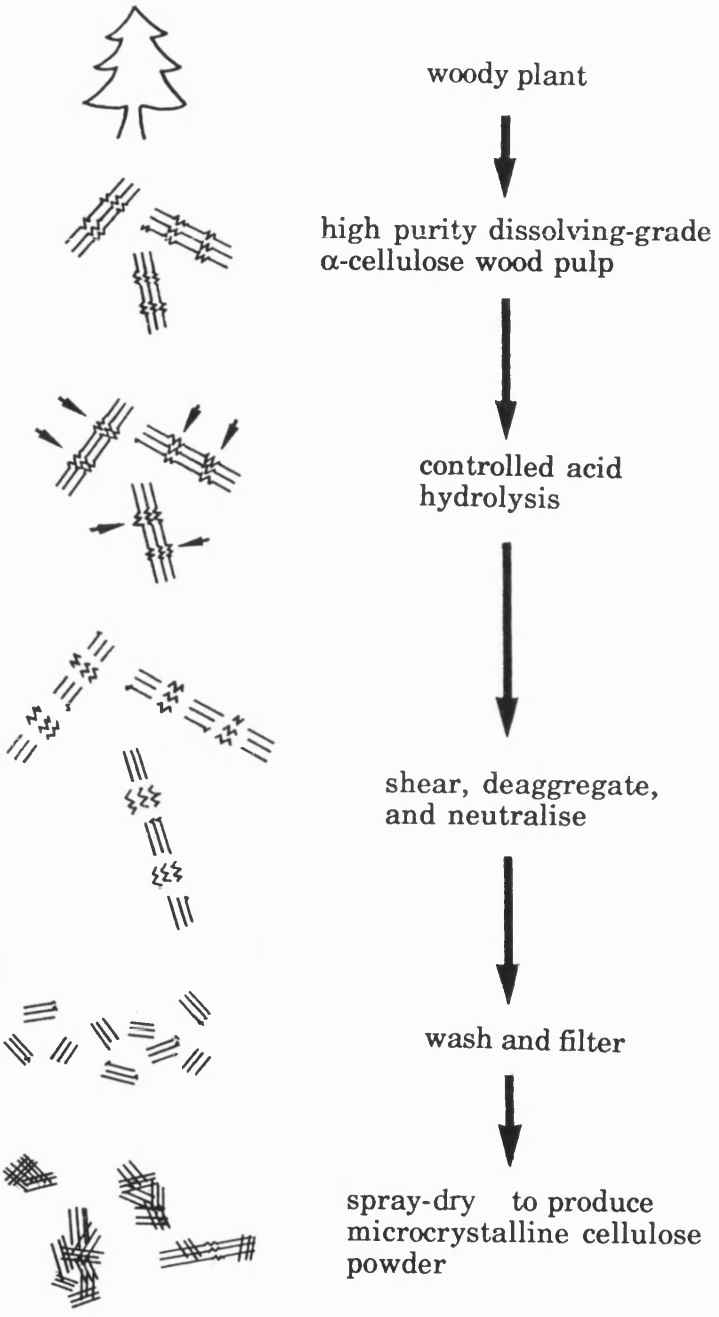


Figure 1.4 Schematic diagram showing the stages involved in the manufacture of microcrystalline cellulose.

'Avory', whichis a block of MCC exhibiting higher density and strength in comparison with blocks dry-compacted from the spray dried product (Battista & Smith, 1962; Battista, 1965). It was suggested that during drying of the gel the numerous hydroxyl groups on the crystallite surfaces which were revealed by the hydrolysis process enabled adjacent microcrystals to bond extensively, the high density of bonds imparting great strength to the product (Battista & Smith, 1962; Battista, 1965).

1.5.4 Characteristics of ungranulated MCC

1.5.4.1 Compaction characteristics

MCC is generally regarded as exhibiting the highest compressibility and compactibility of commonly used direct compression fillers / binders (Mendell, 1972b; Bolhuis & Lerk, 1973; Paronen, 1986). It has been demonstrated that Avicel PH-101 particles undergo a high degree of plastic deformation during compaction (David & Augsberger, 1977; Krycer et al, 1982b; Rees & Rue, 1978b). This property has been attributed to the presence of a large number of slip planes and dislocations within particles arising from the manufacturing process (Reier & Shangraw, 1966; Lamberson & Raynor, 1976). Particle deformation results in microcrystal surfaces being brought in close proximity allowing extensive intermicrocrystal hydrogen bonding (Reier & Shangraw, 1966; Hüttenrauch, 1971; Karehill & Nyström, 1990). MCC also undergoes recoverable deformation during compaction (Aulton et al, 1974; Krycer et al, 1982b; Patel & Staniforth, 1985). However, the formation of interparticulate bonds during compaction limits the disruptive effects of elastic recovery on decompression (Krycer et al, 1982b). Furthermore, it has been demonstrated that particle fragmentation also occurs during compaction (Khan & Rhodes, 1975; Sixsmith, 1982), although it is unlikely that fragmentation is the dominant deformation mechanism (Krycer et al, 1982b). It has been proposed that mechanical interlocking of the irregular and approximately rod-shaped MCC particles is partly responsible for the bonding within compacts (Bolhuis & Lerk, 1973; Karehill & Nyström, 1990b). However, from consideration of the generally rapid disintegration characteristics of MCC tablets and the small size of individual particles, Lamberson & Raynor (1976) suggested that particle interlocking is unlikely to contribute significantly to bonding within MCC compacts.

1.5.4.2 Disintegration characteristics of MCC compacts

Although insoluble, compacts prepared from directly compressed MCC generally exhibit rapid disintegration in aqueous solutions. The hydrophilic character of MCC allows rapid penetration of the surrounding solution via capillary pores in the tablet, penetrated water subsequently effecting disruption of interparticulate hydrogen bonds (Reier & Shangraw, 1966; Lamberson & Raynor, 1976; Lerk et al, 1979). Increasing the compaction force and thus tablet density and interparticulate bonding, however, results in reduced MCC tablet disintegration time (Khan & Rhodes 1972; Khan et al, 1983).

1.5.4.3 Bulk density and flow characteristics of MCC

MCC exhibits poor flow characteristics in comparison with other commonly used direct compression excipients with the possible exception of starch (Mendell, 1972b; Bolhuis & Lerk, 1973). Several factors have been suggested to be responsible for the poor flow characteristics of MCC; its fibrous particle shape (Bolhuis & Lerk, 1973; Marshall & Sixsmith, 1976), small particle size (Marshall & Sixsmith, 1976), and low bulk density (Khan & Rhodes, 1976). In general, grades of MCC possessing a larger mean particle size have been noted to exhibit improved flow characteristics over the grades with a smaller mean particle size (Marshall & Sixsmith, 1976; Doelker et al, 1987a). Although the bulk density and flowability of MCC may be improved by the addition of magnesium stearate (Bolhuis & Lerk, 1973), magnesium stearate reduces the strength of tablets produced (Bolhuis & Lerk, 1973; Doelker et al, 1987a; Jarosz & Parrott, 1984). Alternative flow-aids reduce the strength of MCC tablets by varying degrees (Jarosz & Parrott, 1984).

1.5.4.4 Water vapour adsorption characteristics

As discussed in section 1.3.1.5, anhydroglucose units within crystalline regions of cellulose are unable to adsorb moisture. Water adsorption is thus confined to the anhydroglucose units in the 'accessible' or amorphous regions and on crystallite surfaces. Nikitin (1966a) classified adsorbed moisture into two types depending on its degree of interaction with cellulose; a) tightly bound moisture which formed hydrogen bonds with anhydroglucose units on cellulose chains, and b) free moisture which had condensed inside the cellulosic structure without a thermal effect. Hatakeyama et al (1983) suggested the presence of an additional

intermediate type of moisture adsorbed by amorphous cellulose which, unlike the tightly bound moisture, may be frozen but which does not have the mobility associated with free moisture. More recently, evidence suggesting that moisture adsorbed onto MCC may similarly be described by three states has been discussed by Zografi et al (1984), Zografi & Kontny (1986) and Sadeghnejad et al (1986). Further, approximately the first 3 $\%^{w}/_{w}$ adsorbed moisture was considered to be tightly bound, between approximately 3 and 6 $\%\ ^{w}/_{w}$ adsorbed moisture less tightly bound, and higher concentrations of adsorbed moisture molecules condensed onto previous adsorbed layers behaving like bulk water (Zografi et al, 1984; Sadeghnejad et al, 1986).

Equilibrium moisture adsorption - desorption isotherms (Hollenbeck et al, 1978; Nyqvist & Nicklasson, 1983; Bangudu & Pilpel, 1985: Khan & Pilpel, 1986) and moisture adsorption isotherms alone (Sadeghnejad et al 1986, Khan & Pilpel 1987) have been obtained for Avicel PH-101. Furthermore, the adsorption isotherms for Avicel PH-101 and PH-102 have been reported to be similar (Nyqvist & Nicklasson, 1983; Sadeghnejad et al, 1986). Sorption - desorption isotherms for water onto MCC have been found to show some degree of hysteresis, with more moisture being associated with the cellulose during desorption than during sorption under the same conditions (Hollenbeck et al, 1978; Nyqvist & Nicklasson, 1983; Bangudu & Pilpel, 1985; Khan & Pilpel, 1986).

1.5.4.5 Effect of adsorbed moisture on compaction characteristics

A progressive increase in the moisture content of Avicel PH-102 from 0.6 to 7.3 $\%^{w}/_{w}$ has been found to increase the strength of tablets produced from formulations containing 97% MCC when tablets were prepared at similar relative pressures (Khan et al, 1981). Similarly, a progressive increase in the moisture content of Avicel PH-101 from 0.2 to 6.9 $\%^{w}/_{w}$ was reported to result in an increase in the strength of tablets produced to similar relative densities (Nyqvist & Nicklasson, 1983). It was suggested that increasing the concentration of adsorbed moisture between these levels increases the plasticity of MCC particles by disrupting some of the cellulose - cellulose bonds (Khan et al, 1981) thereby reducing particle yield pressure (Fassihi, 1988). However, a further increase in the moisture content of Avicel PH-101 to 8 - 8.2 $\%^{w}/_{w}$ results in a decrease in the strength of tablets produced, perhaps due to hydrostatic resistance to consolidation

exerted by bulk water (Ragnarsson & Sjogren, 1985; Fassihi, 1988).

1.5.4.6 Specific surface area; comparison between accessibility to water and nitrogen molecules

According to the B.E.T. theory (Brunauer et al, 1938), at very low relative pressures, adsorption of molecules of a gas first occurs at highly energetic sites on the sample surface. If the adsorbate pressure is allowed to increase, the surface of the solid becomes progressively coated with adsorbate molecules and the probability that an adsorbate molecule will adsorb onto a previously adsorbed molecule increases. Thus, second and higher layers of adsorbate may be formed prior to complete surface coverage of the solid, and no pressure actually exists at which a singularly monomolecular surface coverage occurs. However, analysis of adsorption isotherms using the B.E.T. equation (equation 1.1) enables the weight (W_m) of a monomolecular film of adsorbate to be determined, even though a monomolecular layer is never actually separately formed.

$$\frac{P/P_o}{W(1 - P/P_o)} = \frac{1}{W_m C} + \frac{(C - 1)}{W_m C} \times \frac{P}{P_o} \qquad \text{Equation 1.1}$$

where:-

W = mass of gas adsorbed at pressure P

W_m = mass of gas adsorbed as a monomolecular layer

P = partial pressure of adsorbate

P_o = saturation pressure of the adsorbate at the experimental temperature

C = a constant related to the difference between the heat of vaporisation of a monomolecular layer and the heat of vaporisation of the adsorbate

Thus in accordance with the B.E.T. relationship, a plot of P/P_o divided by $W(1 - P/P_o)$ against P/P_o yields a straight line. This relationship, however, is only generally valid in the approximate relative pressure range 0.05 to 0.35 (Lowell & Shields, 1984a). From the B.E.T. isotherm the value of W_m is obtained as the reciprocal of the sum of the slope and the intercept. The sample specific surface area available for contact with the adsorbate can be calculated from the following relationship;

$$\text{Specific surface area} = \frac{W_m \; N_o \; A_{cs}}{M \; X} \qquad \text{Equation 1.2}$$

where:-

N_o = Avogadro's number (6.02×10^{23})

A_{cs} = the cross sectional area of one molecule of the adsorbate

M = the molecular mass of the adsorbate

X = the sample mass

The B.E.T. specific surface area of cellulose fibres (Merchant, 1957; Stone & Scallen, 1965) and Avicel MCCs (Hollenbeck et al, 1978; Nakai et al, 1977a; Sadeghnejad et al, 1986) determined from water vapour adsorption data is approximately 100 to 200 times greater than the area determined from nitrogen adsorption data even though water molecules are larger than nitrogen molecules. This difference is widely interpreted as evidence for the ability of water molecules not only to bond with unbonded-cellulose hydroxyl groups on the physically accessible surfaces, but also the ability of water molecules to disrupt cellulose-cellulose hydrogen bonds within amorphous regions revealing hitherto unexposed microcrystal surfaces and penetrating the structure of both unhydrolysed cellulose (e.g. Nissan, 1978; Caulfield, 1980) and MCC (Zografi et al, 1984; Sadeghnejad et al, 1986). The network of bonding within crystalline regions sets a limit to this process of disruption (Nissan, 1978). However, on desorption of water the capillary network created by adsorbing moisture collapses, although the water-swollen structure may be partially preserved in the dry state by dewatering water swollen MCC by solvent exchange (discussed further in section 7.2). In general, as the polarity of the adsorbate is decreased, the ability to disrupt intermolecular bonding within the cellulose is reduced (Merchant, 1957). Hence nitrogen adsorption only occurs on the presented physical cellulose surfaces such as outer fibre surfaces and existing internal voids. Cellulosic surface area values derived from analysis of nitrogen adsorption data may thus be considered to represent the true internal and external physical surface area whereas values derived from water adsorption represent the hydratable surface area. Further evidence for differences between the phenomena responsible for nitrogen and water vapour adsorption has been provided by Sadeghnejad et al (1986) who reported that for different samples of microfine and microcrystalline cellulose, an

increase in the surface area determined from nitrogen adsorption does not necessarily result in an increase in the surface area determined from water vapour adsorption.

1.5.5 Wet granulation of MCC

1.5.5.1 Aqueous granulation of MCC

Although originally intended for use as a direct compression binder or a dry compression aid when added to dried granules, reports in the literature indicate that MCC is also widely included in wet massed formulations (e.g. Chowhan & Amaro, 1988; Unvala et al, 1988; D'Alonzo et al, 1990). Sheth et al (1980) suggested that the inclusion of MCC in wet granulated formulations reduced the sensitivity of such formulations to inadvertent over-wetting which results from excess granulation fluid addition. In addition, MCC is an important formulation aid for the preparation of drug loaded beads where its presence in the wet massed formulation aids attainment of a suitable consistency for extrusion and subsequent spheronisation (Reynolds, 1970; Fielden et al, 1988).

The effect of water content on the rheological characteristics of MCC-water wet masses has been investigated by Alleva & Schwartz (1986), Rowe & Sadeghnejad (1987), Hancock et al (1991), and Staniforth et al (1988). In all of the aforementioned studies it was reported that as the water content was progressively increased, the wet mass exhibited increased cohesiveness up to a limiting water concentration. Thereafter, an increase in water content resulted in a progressive reduction in product cohesiveness. A similar effect was reported on granulation with aqueous solutions of polyvinylpyrrolidone and hyroxypropyl methylcellulose, although addition of dissolved substances and the concentration in which they were used was found to affect the maximum torque and the liquid required to achieve maximum torque (Parker et al, 1990). Alleva & Schwartz (1986) and Rowe & Sadeghnejad (1987) suggested that the observed increase in wet mass cohesiveness with increased water content may be attributed to the progressive filling of pores by added water through the pendular, funicular and capillary states proposed by Newitt & Conway-Jones (1958). At maximum cohesiveness, it was suggested that the wet mass was in the capillary state, that is exhibiting the characteristics of a thick paste with all the air spaces filled with water. Since the intragranular pores were completely filled, an increase in the

water content of the wet mass above the capillary state resulted in the wet mass moving into the droplet state which corresponded to the formation of a slurry and a decrease in the cohesiveness of the wet mass (Alleva & Schwartz, 1986; Rowe & Sadeghnejad, 1987; Hancock et al, 1991). In the studies presented by Alleva & Schwartz (1986), Rowe & Sadeghnejad (1987) and Hancock et al (1991), the amount of water added at the maximum cohesiveness ranged between approximately 53 % and 67 % expressed as a percentage of water in the final wet mass for different studies; the small differences in the water level required to achieve maximal granule cohesion between studies was presumably at least in part due to differences in the experimental techniques. Furthermore, the amount of water added to achieve maximum cohesiveness and the torque at different water levels was found to be dependant on the commercial form, grade and batch of MCC investigated (Rowe & Sadeghnejad, 1987) which may also explain the slightly different water levels reported by various workers for maximal wet mass cohesion. Using a modified shear cell, Staniforth et al (1988) and Heng & Staniforth (1988), however, reported that the force required to cause shear failure was maximum at water levels corresponding to approximately 17 to 23 % water in the wet mass. The markedly lower value for water level at maximal wet mass cohesion reported by Staniforth et al (1988) and Heng & Staniforth (1988) in comparison with that obtained by Alleva & Schwartz (1986), Rowe & Sadeghnejad (1987) and Hancock et al (1991) may be due to differences in the experimental technique; the comparatively low shear used in the studies by Staniforth et al (1988) and Heng & Staniforth (1988) for preparing the wet masses may have resulted in incomplete intraparticulate wetting. Further, the action of high shear granulation as used in the studies by Rowe & Sadeghnejad (1987) and Hancock et al (1991) is to produce bed dilation which can accommodate larger concentrations of water in larger intergranular voids. In the work reported by Heng & Staniforth (1988), the wet mass was consolidated prior to measurement further reducing interparticle void volume.

Wet granulation has been reported to adversely affect the compactibility of MCC, with a progressive increase in the amount of granulation fluid up to 28.5 $\%^{w}/_{w}$ water in the wet mass resulting in a progressive reduction in the compactibility of Avicel PH-101 and Emcocel 50M (Burrage, 1987). Similarly, using gelatinised starch solution as the granulation fluid, Staniforth et al (1988) reported a reduction in the compactibility of Avicel PH-101 and Emcocel 50M

following wet granulation with 27.1 $\%^{w}/_{w}$ water in the wet mass. Increasing the proportion of fluid used to granulate Emcocel from 27.1 to 31.7 $\%^{w}/_{w}$ water in the wet mass resulted in a further decrease in compactibility (Staniforth et al, 1988). In the studies by Burrage (1987) and Staniforth et al (1988), at equivalent granulation fluid levels, Avicel PH-101 was found to exhibit a greater loss in compactibility in comparison with Emcocel 50M as a result of granulation. Differences between the effect of granulation on the relative reduction in compactibility of Avicel PH-101 and Emcocel 50M were found to be reflected in variations between their relative cohesiveness as determined using a modified shear cell in the presence and absence of water (Heng & Staniforth, 1988; Staniforth et al, 1988). In addition, the reduction in compactibility resulting from granulation was accompanied by an increase in granule poured and tapped bulk densities and an apparent increase in the granule density as assessed using electron micrograph images. (Staniforth et al, 1988). It was suggested that during compaction, much of the energy supplied was used to disrupt the granule structure (Staniforth et al, 1988). Thus, in comparison with ungranulated MCC, granules underwent less useful plastic deformation during compaction which resulted in the formation of a lower interparticulate contact area and bonding at equivalent compaction forces (Staniforth et al, 1988). Differences between the compactibility of ungranulated and granulated MCC were not, however, apparent from the ratio of permanent to recoverable deformation during creep testing (Staniforth et al, 1987). Chowhan & Amaro (1988) reported that increasing the proportion of intragranular MCC reduced the maximum attainable tablet strength for a wet granulated formulation which included a water soluble drug, corn starch, and povidone. It was suggested by the authors that the microporous structure of MCC was reduced by granulation as a result of crystallisation of dissolved solids inside the pores (Chowhan & Amaro, 1988).

O'Connor & Schwartz (1985) reported that the dissolution of actives from spheronised beads prepared with water only from a blend of 20% active and 80% Avicel PH-101 was prolonged. Enezian (1972) stated that following drying, the outer layers of spheronised MCC 'hornify' or harden, although a mechanism by which hornification occurred was not proposed, nor was the phenomenon discussed in any detail. It was, however, stated that the dissolution rate of actives which had been incorporated into the spheres was dependant on the degree of hardening of the outer layer and may be modified by the addition of oil, gum,

starch, glycerin, lactose, or alcohol at the time of formation (Enezian, 1972).

In a study of the effect of lactose type and processing methods on the quality of granules prepared from microcrystalline cellulose-lactose (25:75) mixtures, Remon & Schwartz (1987) showed that fluidised bed drying resulted in granules having a lower friability and a higher percentage of fines than tray drying. Fluidised bed-dried MCC - lactose granules also exhibited higher bulk and tapped densities than tray-dried granules. This was attributed at least in part to the greater proportion of fines in granules dried by fluidisation. The study did not, however, include an investigation of the relative compactibility of the granules dried using these two techniques. As anticipated, an increase in the total amount of granulating liquid resulted in the production of larger granules with reduced friabilities. An increase in the granulation times also resulted in the formation of less friable granules which exhibited a narrower particle size distribution. In addition, granule friability could be reduced and particle size increased by pre-dissolution of 10% of the lactose previously used as a dry binder in the granulating fluid.

1.5.5.2 Non-aqueous granulation of MCC

The effect of granulating MCC formulations with ethanol or mixtures containing different concentrations of ethanol in water on the characteristics of the spheronised product have been studied (Millili & Schwartz, 1988). These workers found that decreasing the ratio of ethanol to water resulted in a reduction in the dissolution rates of the spheronised products, and decreased their friability and porosity. In addition, it was noted that spheres prepared using 95% ethanol exhibited superior compressibility when compared with spheres prepared from granulation with water alone. However, possible reasons for the improvement in compression characteristics following granulation with increased proportions of ethanol to water were not presented.

1.6 Aims and objectives

The principle aims of the present study were to characterise and explain the effect of wet granulation on the physico-mechanical characteristics, in particular the compaction properties, of MCC. Further, methods by which the adverse effects of wet granulation on the mechanical characteristics of MCC could be reduced were investigated.

Chapter 2. Characterisation of ungranulated MCC and general methods used for powder and granule characterisation

2.1 Materials

Unless otherwise stated, MCC refers to Emcocel 50M, lot number 8259 (Edward Mendell Co Inc., Patterson, New York, U.S.A.). In addition MCC from an alternative source; Avicel PH-101, lot number 6547 (F.M.C. Corp., Philadelphia, USA), was characterised using a selection of techniques. Both MCC s complied with USP / NF XXI. Where appropriate, samples were removed from commercial bulk MCC powders using the technique of coning and quartering.

2.2 Methods

2.2.1 Particle size analysis and particle size separation

Particle size distributions were determined and particles separated according to size using a sieving technique. MCC powder was sieved in 25 - 30 g lots on a stack of Test Sieves (Endecotts Ltd., London, U.K.) complying with B.S. and I.S.O. specification. The nominal aperture diameters of sieves used were 180 μm, 90 μm, 75 μm, 63 μm, and 45 μm. In addition, particles having a sieve diameter below 45 μm were collected. The sieve stack was mechanically vibrated (Fritsch Analysette, Christison Scientific, Gateshead, U.K.) for 15 minutes at a nominal instrument amplitude of 4. Each sieve and the collector was weighed before and after sieving and material retained determined by difference. The particle size distribution was determined from the mean weight of particles remaining on each sieve and in the collection tray following four separate sieving procedures using different powder samples. The median particle diameter and the diameters corresponding to the upper and lower quartile points were determined graphically. In some of the analytical techniques described below, particles with a sieve diameter 125μm to 180 μm were used. The latter were obtained by sieving particles collected on the 90μm sieve through a 125 μm sieve for 15 minutes using a methodology similar to that described above.

Cleaning of sieve meshes following sieving was found to be difficult since particles lodged in the meshes could not be removed by dissolving in a commonly used solvent. For this reason, the following cleaning procedure was adopted

between each set of 4 sieving procedures. Firstly, sieves were partially cleaned by gentle brushing on the underside of the mesh. Secondly, since it was found that almost all of the remaining particles could be loosened or dislodged from the mesh by immersion in an ultrasonic bath (Model FS 200, Decon Ultrasonics Ltd., Sussex, U.K.) containing distilled water, this sonication procedure was carried out for 5 to 10 minutes. Finally, following drying a second gentle brushing of the underside of sieves was carried out.

2.2.2 Scanning Electron Microscopy

Samples were mounted on aluminium specimen stubs using double-sided adhesive tape and sputter coated with gold (Sputter Coater, Model S150B, Edwards High Vacuum, Sussex, U.K.). To avoid charring of the MCC samples, coating was carried out for two 3 - 4 minute periods using a chamber pressure of 6 mbar between which samples were allowed to cool. Scanning electron microscope studies (JSM 35C, J.E.O.L., London, U.K.) were carried out using an incident beam of 15 kV which was selected in order to avoid specimen damage.

2.2.3 Specific surface area available to nitrogen

Specific surface area was determined by B.E.T. analysis of nitrogen adsorption behaviour (section 1.5.4.6) on a known weight of sample at a temperature close to the boiling point of the adsorbate. In the present study, two dynamic methods and one volumetric method was used to determine quantities of nitrogen adsorbed at different relative pressures. Prior to each surface area determination, samples were degassed in order to remove adsorbates such as moisture. The three experimental methods differed with respect to the sample degassing procedure as well as the instrumentation used as described below.

Method A

Specific surface area was determined using a dynamic (continuous flow) method (Autosorb-1 Sorption System, Quantachrome Corp., Greenvale, New York, U.S.A.). Samples were degassed at room temperature under vacuum for 24 hours. Surface area data were obtained using 5 different relative pressures of nitrogen. The nitrogen was mixed with helium, an inert noncondensible carrier gas, using a nitrogen concentration in the mixture in the range 5 to 30 %. Results were analysed using the multipoint B.E.T. method. Replicate determinations were not performed.

Method B

Specific surface area determinations were again performed using a dynamic method (Quantasorb, Quantachrome Corp., Green Vale, New York, U.S.A.). In this method, sample degassing was achieved by continuous purging of the sample with dried nitrogen for three to four days at room temperature. Data were obtained using three different relative pressures of nitrogen corresponding to a concentration of 10, 20 and 30% of nitrogen in helium mixtures. The results were analysed using a multipoint B.E.T. equation. Replicate determinations using additional samples were performed for a selection of sample types.

Method C

Specific surface area determinations were performed using a volumetric low temperature gas adsorption apparatus (Orr analyser model 2100D, Micromeritics Instrument Corp., Norcross, Georgia, U.S.A.). Using a sample weight of 3 g, samples were degassed at 70°C whilst under a vacuum of 13 Nm^{-2} for 4 hours. Samples were transferred to the surface area analyser and degassing was continued at 50°C for a further 12 hours under vacuum applied by an oil diffusion pump (actual pressure unknown). A minimum of 15 data points for nitrogen adsorption over the relative pressure range 0.05 to 0.2 were measured. Specific surface area analyses were repeated four times for each material type using different samples.

2.2.4 Mercury porosimetry

Pore size distributions were determined using mercury intrusion porosimetry (Pore Sizer 9300, Micromeritic Instrumental Corp., Norcross, Georgia, U.S.A.). Powder samples having a sieve diameter 125 to 180 μm and a mass of approximately 0.5 g were dried by storage under reduced pressure over silica gel and subsequently accurately weighed into the sample cell. Atmospheric gases from the pore space within samples were removed by application of a vacuum (less than 10 Nm^{-2}). Hypobaric analysis was performed by allowing incremental volumes of mercury into the sample at a series of pressures. Hyperbaric analysis of pores having diameters less than approximately 10 μm were performed by forcing mercury into the sample hydraulically using a series of pressures greater than atmospheric pressure. In the case of either hypo- or hyperbaric analyses, the volume of mercury intruded was recorded at each

pressure increment. Assuming that pores within samples were cylindrical, the pore diameter above which pores were filled was determined using equation 2.1.

$$D_p = \frac{-4\gamma\cos\theta}{P} \qquad \text{Equation 2.1}$$

where:-

D_p is the pore diameter

γ is the surface tension of mercury (= 0.474 Nm^{-1})

θ is the contact angle between mercury and the sample (assumed to be 130°)

P is the pressure applied to the mercury

Results are presented as the differential pore volume per sample mass (specific pore volume) as a function of the pore diameter. The latter provides information regarding the total volume of pores at each diameter. In addition, the inter- and intragranular porosity was estimated from plots of the cumulative intrusion as a function of the pore diameter. Although it was considered that the use of 125-180 µm particle size fraction (the largest available for all sample types) for the analyses would aid distinction between interparticle voids and interparticle pores, a large inflection point in porosimeter plots was not found around the anticipated largest pore diameter. This presented difficulties in distinguishing between interparticle voids and intraparticle pores. However, a slight inflection in the cumulative volume curve at a pore diameter of 10 µm was observed and this diameter was therefore selected as the changeover point between filling of inter- and intraparticulate pores. This diameter was also considered a structurally valid value from examination of scanning electron micrographs of particles (figure 3.2). Intraparticle porosity was thus defined as the cumulative volume of mercury intruded below a pore size of 10 µm. Replicate determinations using additional samples were only performed for selected sample types.

2.2.5 True density

Powder true density was determined using helium pycnometry (Multipycnometer, Quantachrome Corp., Green Vale, New York, U.S.A.). Approximately 1.5g of MCC powder was accurately weighed into the sample cell. Helium gas was used to pressurise the sample chamber and the pressure recorded.

An additional volume was connected to the sample cell and the subsequent pressure recorded. From the pressure readings and the volumes of the sample cell and the additional volume, the true volume of the sample was determined. The true density was calculated by dividing the mass of the sample by the sample volume.

2.2.6 Bulk density

Poured bulk volume was determined using a standardised method. MCC powder was poured through a glass powder funnel into a pre-weighed 50 cm^3 volume glass measuring cylinder. The poured (fluff) bulk density, ρ_o, was calculated by dividing the sample mass by the poured volume. Measurements were repeated five times using different samples enabling a mean value for ρ_o to be determined.

Following each determination of poured bulk density, the cylinder and its contents were tapped 1,000 times using a jolting volumeter (STAV 2003, J. Engelsmann, Germany) and the new volume occupied by the MCC powder was measured. Further tapping beyond 1,000 taps resulted in a negligible change in volume. The tapped bulk density, ρ_t, was calculated by dividing the sample mass by the volume following 1,000 taps. Measurements were repeated five times using separate powder samples enabling a mean value for ρ_t to be determined.

2.2.7 Packing geometry and flowability

The compressibility index (Carr, 1970) and Hausner ratio (Wells & Aulton, 1988) were determined from ρ_t and ρ_o using the following relationships:

$$\text{Carr's compressibility index} = \frac{\rho_t - \rho_o}{\rho_t} \times 100 \qquad \text{Equation 2.2}$$

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_o} \qquad \text{Equation 2.3}$$

In addition, the coefficient of tablet weight variation for a minimum of 40 compacts (section 2.2.8 immediately below) prepared at an upper punch force of approximately 15 kN was used used to compare the flowability of materials.

2.2.8 Tablet preparation

Material for compaction was stored for a minimum of 7 days in thin layers in a constant temperature cabinet maintained at approximately 50 % relative humidity and 25°C. Prior to tableting, conditioned material was mixed for 3 minutes in a polythene bag.

Tablets were prepared using a single station reciprocating tablet press (Type F3, Manesty Machines Ltd., Speke, U.K.) fitted with 8mm diameter flat-faced punches. The machine was operated under power at a compression rate of approximately 52 cycles per minute. In order to monitor the upper punch force applied during compaction, the upper punch holder was modified to accommodate a piezoelectric load cell (Type; 9031, Kistler Instruments, Hants., U.K.) and an associated force distribution washer immediately above the upper punch. The retaining screw normally used was removed and the upper punch was held in place by a retaining collar secured to the underside of the punch holder using Allen bolts. The collar was designed to allow unhindered transfer of applied forces to the distribution washer and load cell with minimal force losses. Figure 2.1 is a schematic diagram of the main features of the modified upper punch assembly. The load cell was pre-calibrated by the supplier and used with a pre-matched charge amplifier (Type; 5054A 1010, Kistler Instruments, Hants., U.K.) which converted the change in capacitance induced in the load cell by the applied force into a voltage suitable for the data capture system. The latter comprised a specially constructed analog to digital converter which was connected to a personal computer (Model B, British Broadcasting Corporation Microelectronics, Acorn Computers Ltd., Cambridge, U.K.). The peak upper punch force applied during each compaction was recorded using a printer. The complete data collection system is summarised in figure 2.2.

Tablets were prepared at a series of compaction forces, usually five, in the range 4 to 28 kN. The target compression weight was 175 mg. In an attempt to avoid fluctuations in the feed rate of material to the die, material was manually transferred into the feed shoe using a small scoop, and the shoe was refilled at regular intervals so maintaining the shoe more than half full throughout. No attempt was made to control laboratory humidity during tableting. However, since the moisture content of MCC is known to affect its compactibility (section 1.5.4.5), in studies where direct comparison of samples of MCC, some of which

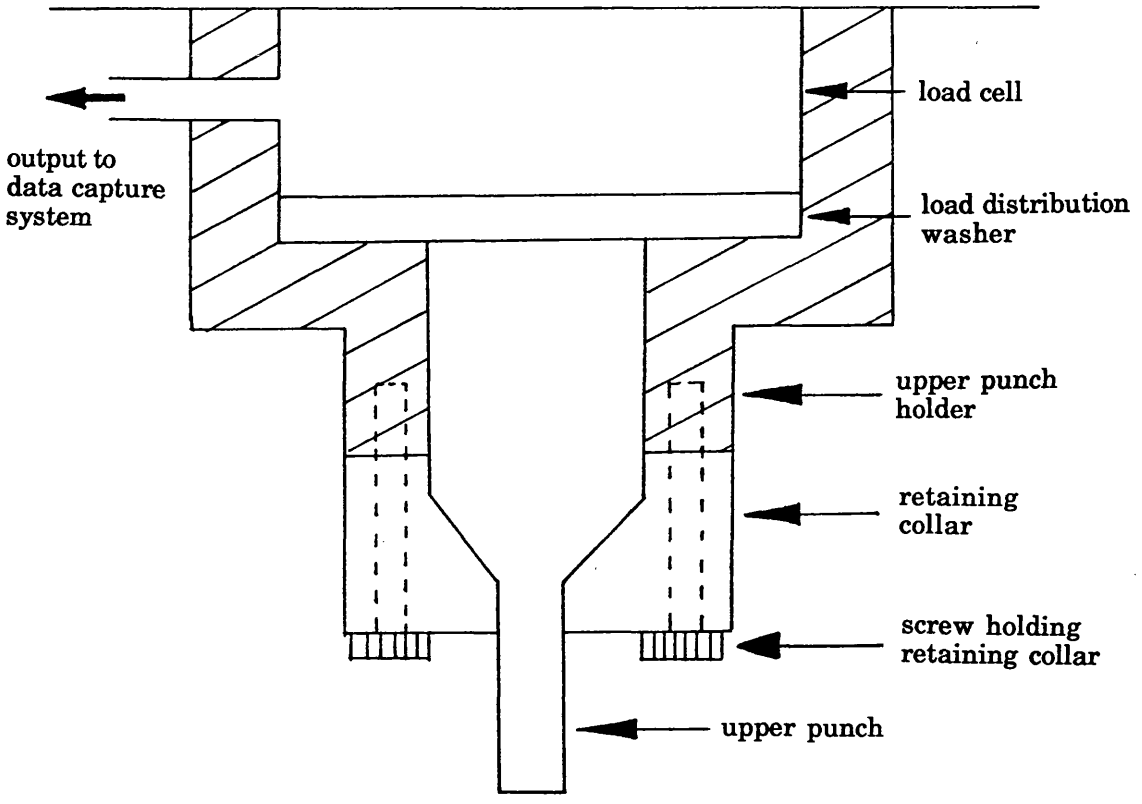


Figure 2.1 Schematic diagram showing modifications to upper punch assembly enabling upper punch forces applied during compaction to be monitored.

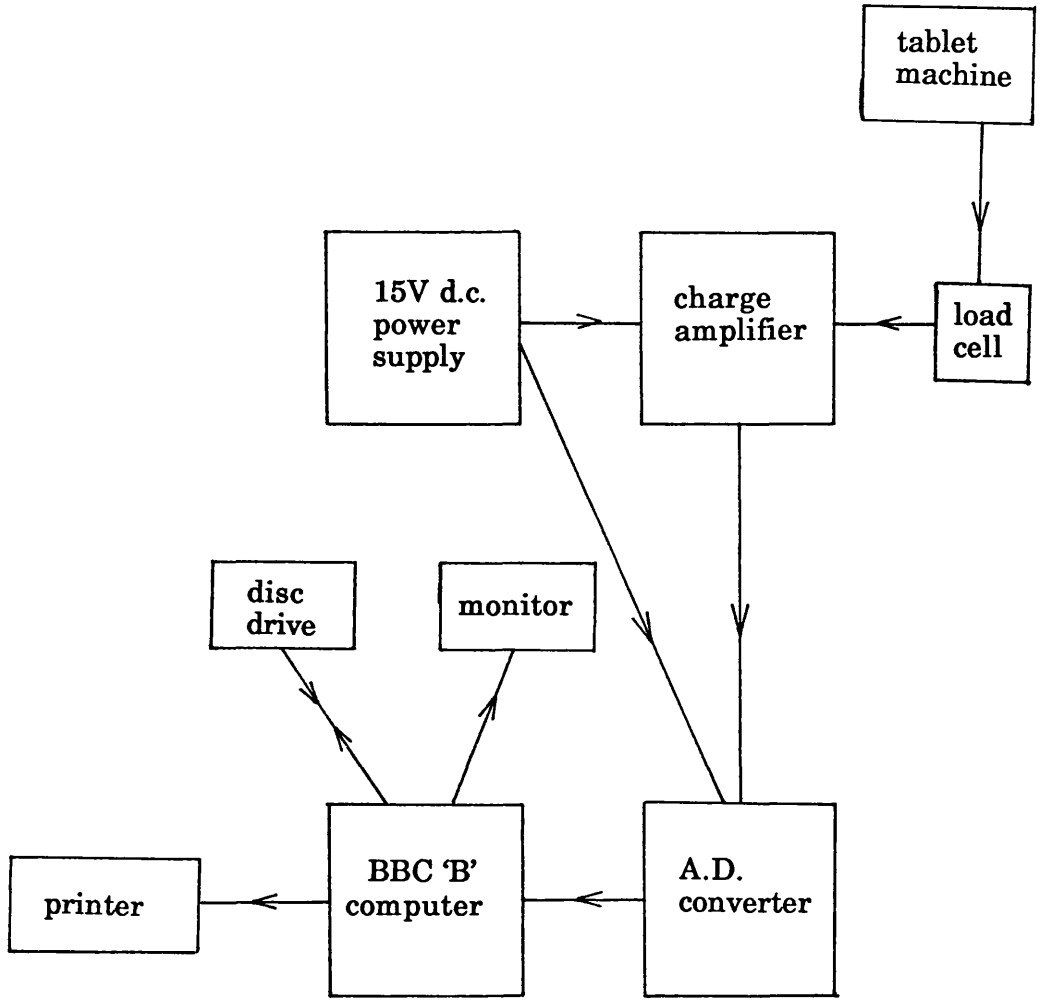


Figure 2.2 Block diagram indicating the complete system for determination of force applied during tablet compaction.

had been treated, was intended, where possible the samples in question were compacted on the same day in an attempt to minimise the effects of possible wide variations in room temperature and humidity. In addition, it was considered that re-setting up the tablet machine instrumentation, which was necessary when changing punches for other laboratory work, could affect the force recorded by the load cell during compaction since slight alterations in the alignment of the upper punch arrangements may occur. Thus, punches and associated instrumentation were not changed between samples for which the compaction characteristics were to be directly compared with each other. With the exception of tablets prepared as part of the investigations described in Chapter 5, in the case of ungranulated MCC, tablets were only prepared on one occasion and the profiles generated were used as a comparison with all other granulated tablet profiles in subsequent investigations. This was considered reasonable since ungranulated MCC had a substantially higher compactibility in comparison with granules evaluated in subsequent investigations.

Materials were compacted without the addition of glidants or lubricants since it has been reported elsewhere that the presence of such excipients introduces interactions which influence the compactibility of MCC (section 1.5.4.3) and might therefore mask the effects due to granulation studied here since their addition may not affect all MCC materials under investigation in the present study to a similar extent. Furthermore, it was found that all samples exhibited low sticking to the punches and die, a phenomenon also reported by Bolhuis & Lerk (1973), and did not therefore require lubrication. However, the poor flow characteristics of ungranulated MCC also reported elsewhere (section 1.5.4.3) necessitated additional vibration of the feed shoe in order to achieve satisfactory die filling and acceptable consistency of tablet weight. This was carried out using a hand-held column packing vibrator. After ejection from the die, tablets prepared from all materials were collected in sequence on a specially constructed perspex chute which queued tablets. Use of the collection chute enabled the force at which individual tablets had been compressed to be identified. Tablets were equilibrated at 53% relative humidity and 25°C for between 7 and 28 days before testing.

2.2.9 Mechanical testing of tablets

Only tablets with a weight of 175 mg ± 2 mg and prepared at a compaction force within ± 2.5 % of the mean upper punch force were tested. No

attempt was made to control laboratory humidity during tablet testing. Tablet dimensions were measured using a digital micrometer. The mechanical properties of tablets were determined by diametral loading using a tensile tester (Type T5000, J.J. Lloyd Instruments Ltd., Southampton, U.K.) fitted with a 500 N load cell. The load cell was calibrated by the supplier. The movable upper cross - head was lowered onto the tablet using a strain rate of 1 mm min^{-1}. The force applied across the diametral cross-section of the tablet during loading was continuously monitored using the load cell. In addition, a linear variable displacement transducer (LVDT) between the stationary and moving platens enabled the tablet deformation occurring during tablet failure to be monitored. The LVDT output was previously calibrated using feeler gauges. Both the load cell and LVDT outputs were connected via appropriate amplifiers to an analog to digital converter which was in turn linked to a personal computer (Type; Master, British Broadcasting Corporation Microelectronics, Acorn Computers Ltd., Cambridge, U.K.). The tensile strength (TS) (Fell & Newton, 1970) and the corrected (normalised) work of failure or "toughness" (CWF) (Rees & Rue, 1977 and 1978a) of tablets were determined from the relationships shown in equations 2.4 and 2.5 :-

$$\text{Tensile strength} = \frac{2P}{\pi D t} \qquad \text{Equation 2.4}$$

where:-

P = Peak force required to cause tensile failure

D = Diameter of the compact

t = Thickness of the compact

$$\text{Corrected (normalised) work of failure} = \frac{2}{\pi D t} \int_{o}^{x\,max} F_{max} \cdot dx \qquad \text{Equation 2.5}$$

where:-

D = Tablet diameter

t = Tablet thickness

F_{max} = Peak force required to cause tensile failure

x = Tablet deformation

x max = Total tablet deformation at failure

Visual assessment of tablets during and following breaking indicated that most tablets failed in tension. However, some - particularly those made at the lower forces - underwent squashing at the tablet surfaces in contact with the upper and lower platens rather than achieving ideal line loading.

Mechanical testing was performed on ten tablets prepared at each upper punch force. Tablet tensile strength and corrected work of failure were plotted against maximum applied upper punch force during compaction and were used as the basis for comparing the relative compactibility of subsequent product types. Profiles were generated using a software package, Genstat 5, specially modified for the purpose. Mean compaction data values together with 95% confidence intervals were plotted and the best fit line generated through the data. Because statistical analysis was found to exhibit limitations with respect to assessing practical differences between the compactibility of various products (section 6.3.1), most comparisons of profiles were performed by visual inspection using the criteria that if the 95 % confidence interval bars did not overlap, pairs of curves could be considered significantly different.

2.2.10 Other characterisation techniques

In addition to physico-mechanical characterisation by the techniques described above, the particle friability (Chapter 4), moisture content, moisture adsorption characteristics, and surface area available for moisture adsorption (Chapters 9 and 10), degree of crystallinity and polymorphic form (Chapter 11) of ungranulated MCC, and the disintegration time of tablets prepared from ungranulated MCC (Chapter 6) was investigated for specific purposes in relation to testing individual hypotheses. For these reasons, the methods used and the results obtained are described in the relevant chapters.

2.3 Characterisation of ungranulated MCC; results and discussion

2.3.1 Particle size

The percentages of particles in each sieve fraction are given in table 5.2 in Chapter 5. From a cumulative percentage frequency oversize plot, ungranulated MCC was found to have a median particle diameter of approximately 60 μm, the diameters at the upper and lower quartile points being 35 and 80 μm respectively. Using a sieving technique, Whiteman & Yarwood (1988) reported that the median particle diameter was 67 μm which is comparable with the results of the present study.

2.3.2 Qualitative appearance

Scanning electron micrographs of particles in different sieve size fractions of ungranulated MCC are shown in figure 5.1. in Chapter 5. Qualitatively the majority of particles appear to be comprised of smaller, loosely packed structures, the latter presumably fibre fragments obtained as a result of controlled hydrolysis during MCC manufacture (section 1.5.2). In addition, a high proportion of both the component structures and bulk MCC particles are dendritic. However, some particles have the appearance of more spherical, although irregular, masses. Electron microscope studies of Avicel PH-101 were carried out by Marshall & Sixsmith (1974) who also reported the presence of two types of particles; rod like agglomerates and irregular masses. Further, using image analysis to quantify the mean particle shape, Staniforth & Hart (1987) reported that the majority of Emcocel 50M particles were dendritic.

2.3.3 Specific surface area

The specific surface areas, S_w, of ungranulated MCC powder from two different commercial sources are shown in table 2.1, together with information relating to the effect of particle size and the experimental method used.

Table 2.1. The effect of experimental method, particle size distribution, and commercial source on the specific surface area (S_w) of ungranulated MCC (95 % confidence limits in parenthesis).

Source	Particle size distribution	Method	S_w (m^2g^{-1}) (replicates, where obtained, are given)	Mean S_w (m^2g^{-1})
Emcocel	as received	A	1.22	1.22
Emcocel	as received	B	1.29, 1.28	1.29
Emcocel	as received	C	1.76, 1.69, 1.58, 1.58	1.65 (±0.14)
Emcocel	75-90 μm	C	1.83, 1.68, 1.67, 1.58	1.69 (±0.16)
Avicel	as received	C	1.73, 1.61, 1.56, 1.26	1.54 (±0.32)

The two dynamic methods (methods A and B) yielded similar values for S_w which were lower than obtained by the volumetric method (method C). In the present study the higher value for S_w obtained by method C in comparison with method A (table 2.1) may result from the higher temperatures used during degassing under vacuum in method C since Zografi et al (1984) have reported that increasing the temperature from 25 to 100°C during vacuum drying of Avicel reduces the amount of residual moisture adsorbed by the material. Adsorbed moisture may occlude some of the particle pores resulting in lower sample specific surface areas as determined by nitrogen adsorption. Sample degassing by method B involved purging with dry nitrogen gas at ambient temperatures, and was considered unlikely to have resulted in greater moisture removal than vacuum degassing at elevated temperatures as in method C. Thus, the presence of reduced amounts of residual moisture associated with samples characterised by method C was similarly considered to be responsible for the higher values for S_w obtained using method C in comparison with method B. In addition, differences in the values obtained by the three methods for S_w may be a result of differences in the instrument and technique.

It is also noted that determination of surface areas of less than approximately 1 m^2g^{-1} using nitrogen adsorption is subject to inaccuracies (Lowell & Shields, 1984c). The surface area of ungranulated Emcocel obtained in the present study was, however, comparable with the value reported by Zografi et al (1984) for ungranulated Avicel PH-101 using both nitrogen (1.31 m^2g^{-1}) and krypton (1.42 m^2g^{-1}) as the adsorbate gas following sample degassing at 25-50°C under vacuum. In addition, using nitrogen as the adsorbate molecule, Sadeghnejad et al (1986) reported surface area values of 1.22 m^2g^{-1} for Avicel PH-101 powder, and Pesonen & Paronen (1990) reported surface area values of 1.27 and 1.26 m^2g^{-1} for Emcocel 50M and Avicel PH-101 respectively, which is comparable to the results reported here obtained using dynamic techniques.

Further, the data in table 2.1 indicates that selection of a coarse size fraction of Emcocel for surface area analysis had an insignificant effect on the specific surface area in comparison with unfractionated material containing finer size fractions (Student's t test, $P < 0.01$). This suggests a homogeneous processing effect on specific surface area resulting from spray drying which was size independent.

2.3.4 Pore size and pore size distribution

The inter- and intragranular pore size distribution is shown in figure 3.3.a. The principle mode of the intraparticle pore diameter distribution was found to be approximately 3 μm which is consistent with the particle appearance as assessed using scanning electron micrographs (figure 5.1 in Chapter 5).

In the present study using the criterion that pores with a diameter less than 10 μm represented intraparticle pores rather than interparticle pores, the total intraparticle porosity was found to be approximately 0.45 cm^3g^{-1} (table 3.3, mean of two replicate determinations). Using 2 μm as the largest intraparticle pore diameter, Pesonen & Paronen (1990) reported that the intraparticle porosity obtained from mercury intrusion studies for Emcocel 50M and Avicel PH-101 was 0.09 and 0.14 cm^3g^{-1} respectively. Re-calculation of the results obtained in the present study using 2 μm as the changeover diameter between inter- and intraparticle pore filling gave a total intraparticle porosity of 0.07 cm^3g^{-1} which is of the same order of magnitude to that reported by Pesonen & Paronen (1990).

2.3.5 True density

The true density of ungranulated MCC powder (table 2.2) was found to be similar to that reported by other workers for Emcocel 50M using similar techniques to that used in the present study (e.g. Pesonen & Paronen, 1986 and 1990:- 1.52 gcm^{-3}; Doelker at al, 1987a:- 1.54 gcm^{-3}; Whiteman & Yarwood, 1988:- 1.53 gcm^{-3}), and similar to that reported by Stone & Scallen (1965) for unhydrolysed cellulose (1.53 gcm^{-3}).

Table 2.2. True and bulk densities for ungranulated MCC powder (95 % confidence limits provided in parenthesis).

True density	1.54 gcm^{-3}
Poured bulk density	0.25 (± 0.01) gcm^{-3}
Tapped bulk density	0.36 (± 0.01) gcm^{-3}

2.3.6 Bulk density

The poured bulk density of ungranulated MCC powder was found to be similar to that reported for Emcocel 50M by other workers (e.g. Pesonen & Paronen, 1986 and 1990:- 0.23 gcm^{-3}; Doelker et al, 1987:- 0.29 gcm^{-3}). The tapped bulk density was also found to be of similar order of magnitude to that reported by other workers (e.g. Pesonen & Paronen, 1986, 1990:- 0.31 gcm^{-3}; Doelker et al, 1987:- 0.37 gcm^{-3}).

2.3.7 Packing geometry and flowability

The compressibility index and Hausner ratio for ungranulated MCC are given in table 2.3. In accordance with the definitions proposed by Carr (1970), ungranulated MCC may be described as a poorly flowing cohesive powder. The poor flow characteristics of ungranulated MCC were also noted qualitatively during tableting where it was observed that the low bulk density and poor flowability of the material resulted in difficulties in obtaining tablets with the desired weight or within acceptable weight variation tolerances under normal operating conditions. Application of additional vibration to the feed shoe improved the flow characteristics of the excipient enabling production of tablets having the target weight, although a wide weight variation was still obtained (table 2.3 and section 6.3.2).

Table 2.3. Packing geometry and flowability of ungranulated MCC powder.

Carr's compressibility index	30.6 %
Hausner ratio	1.44
Coefficient of tablet weight variation (with additional vibration of the feed shoe)	4.10

2.3.8 Compaction characteristics

The compaction characteristics of ungranulated MCC powder having a size distribution as received and also of MCC powder separated into different size fractions are shown in figure 5.2 (Chapter 5). All ungranulated MCC powder

samples produced tablets having high tensile strength and work of failure profiles. The data is discussed in detail in section 5.3. Although other studies have been carried out to examine the compression characteristics of MCC, most have included additives such as magnesium stearate which are known to modify compressibility. Thus, it is not easy to compare data obtained in the present study with that obtained by other workers.

Chapter 3. A study of the effect of the proportion of water used in wet granulation on the physico-mechanical characteristics of MCC granules

3.1 Objectives

The aims of this part of the study were to investigate the effect of using different ratios of MCC to water during wet massing on the physico-mechanical characteristics of the dried product.

3.2 Methods

3.2.1 Preparation of wet masses

Wet granulations were performed using a domestic food processor (Variomatic, Model FP600, Kenwood Ltd., Havant, Hampshire, U.K.). Wet masses were prepared batchwise using 150 g MCC (Emcocel 50M, lot number 8261, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) and distilled water as the granulation fluid. The weight of water used to prepare each granule batch was varied in the range 55 to 750 g, which corresponded to between 26.8 and 83.3 percentage by weight water in the final weight of wet mass ($\%^{w}/_{w}$). The actual proportions of water used to prepare granules are given in table 3.2 below. The required amount of water was added to MCC over 15 seconds using a consistent granulation speed which was approximately 1000 rev min^{-1} (speed setting 5 on the processor), after which granulation was continued for a further 15 seconds at the same speed. After this time granulation was interrupted to allow any material which had become adhered to the goblet sides to be scraped off and re-added to the wet bulk. Granulation was then continued for a further 150 seconds using a consistent speed of approximately 1450 rev min^{-1} (speed setting 8 on the processor), again interrupting granulation every 30 seconds to re-add material adhered to the goblet sides to the granule bulk.

Where the proportion of granulation fluid was less than or equal to 53.8 $\%^{w}/_{w}$ it was found desirable to pass the wet product through a screen, aperture diameter of 1.7 mm (10 mesh), prior to drying taking care to avoid densification of the wet mass but so as to improve moisture profiling during drying of the wet granule bed. At water levels greater than or equal to 66.6 $\%^{w}/_{w}$ the wet products formed had paste-like or slurry consistencies and wet screening was therefore not performed.

3.2.2 Drying and particle size standardisation

Wet masses were tray dried in layers approximately 15 mm thick in a convection oven (Baird and Tatlock Ltd., Essex, U.K.) at 60°C for 2 hours. After this time products prepared using water levels greater than or equal to 53.8 $\%^{w}/_{w}$ had not reached the drying end point, the latter considered to be the removal of all added water on a weight basis. In such cases, drying was continued under similar conditions but with periodical gentle agitation or breaking of any caked material in an attempt to reduce excessive localised overheating. Drying was continued until the total loss in moisture was approximately equal to the proportion of water which had been added during granulation. All dried products were subsequently allowed to equilibrate under ambient conditions for a minimum of 15 hours after which they were stored in sealed polythene bags prior to testing. Where possible dried granules were passed through a 0.71 mm aperture diameter screen. For dried products prepared from water levels greater than or equal to 53.8 $\%^{w}/_{w}$ it was found necessary to carry out a milling stage using methods described in section 3.2.3 below and table 3.2. before screening. Granules thus prepared were classified according to their sieve diameter using the general method described in section 2.2.1. except that the nominal aperture diameters of sieves used were 250 µm, 180 µm, 90 µm and 75 µm. In addition, a sample of granules having sieve diameters 125 to 180 µm was obtained for use in porosimetry studies. In an attempt to eliminate possible effects on the physico-mechanical characteristics of compacts prepared from these granules caused by differences in particle size distributions (section 5.3), standardised material representative of each granule type was prepared by combining sieve fractions according to an arbitrarily selected standard formula presented in table 3.1, and mixing for three minutes by shaking in a polythene bag.

Table 3.1. Formula for preparation of size standardised granules

Sieve size fraction	Percentage of particles (weight basis)
180 - 250 µm	25.0 %
90 - 180 µm	62.5 %
75 - 90 µm	12.5 %

3.2.3 Milling

Milling was performed on dried granules and granule agglomerates prepared from water levels equivalent to or greater than 53.8 $\%^{w}/_{w}$ solids. This was first attempted using an end runner mill (Beck and Pollitzer, Bristol, U.K.) for a maximum of 15 seconds. In cases where more intense milling was required, a hammer mill (Model DFH 48, Culatti, Glen Creston, Stanmore, U.K.) was employed with a 1.5 mm aperture diameter screen. The method of comminution used for granules prepared using different concentrations of water is indicated in table 3.2.

3.2.4 Preparation of centrifuged wet slurries

Two additional batches of slurries, both containing 80.0 $\%^{w}/_{w}$ water, were prepared using the methods described above (section 3.2.1) except that for one of the batches the granulation time was shortened by 10 seconds for the reason described below. Both batches of slurry were centrifuged for 30 minutes at 8,000 rev min^{-1}. For one of the batches the supernatant was discarded and the concentrated solids dried as described above in section 3.2.2. The loss on drying for the concentrate indicated that the concentrate had a water content of approximately 65 $\%^{w}/_{w}$ following centrifugation. In the case of the other batch which was used as a 'control', the supernatant was re-blended with the concentrated solids in the food processor for 10 seconds using a speed setting of approximately 1450 rev min^{-1} (speed setting 8 on the processor) before drying. In order to keep the overall granulation time consistent and equal to that in the previous experiments, the initial granulation time for this batch was reduced accordingly. Milling, sieving and granule size standardisation (sections 3.2.2 and 3.2.3) were carried out for both centrifuged material types.

3.2.5 Physico-mechanical characterisation of granules

The bulk densities and packing characteristics of granules, size standardised as described in section 3.2.2 above, were determined using the appropriate techniques described in sections 2.2.6, and 2.2.7. Scanning electron microscope studies were performed using particles with sieve diameters between 90 and 180 μm using the method described in section 2.2.2. The inter- and intragranular pore size distribution and intragranular porosity of granules with

sieve diameters between 125 to 180 μm were obtained using the technique described in section 2.2.4. The surface area for size standardised granules was determined using method B in section 2.2.3. In addition, the friability of ungranulated MCC and MCC granules was assessed using a modification of the method described by Krycer et al (1982a). 5 g samples of accurately weighed material having a sieve diameter of 125 to 180 μm were placed on a 125 μm sieve together with 10 hollow plastic balls (approximate diameter 2 cm and individual weight 1 g). The weight of the sieve and contents (MCC material and balls) were recorded before and following shaking for 10 minutes under standardised conditions using a mechanical seive shaker. The particle friability was determined from the mass of MCC powder which passed through the sieve expressed as a percentage of the original sample weight.

Powder X-ray diffractograms for particles with a sieve diameter of 75-90 μm were obtained using a copper target X-ray tube (type; PW 2273/20, Philips) in conjunction with a 4 kW X-ray generator (type; PW 1730/10, Philips). A computer controlled vertical goniometer (type; PW 1820/00, Philips) was used with a xenon proportional counter (type; PW 1711/10, Philips) and diffractometer control (type; PW 1710, Philips). Samples were scanned between 10 and 30 degrees 2 θ, output supplied to a chart recorder (type; PM 8203A, Philips). The percentage of crystalline material, *%Cr*, was estimated from X-ray diffractograms using the method proposed by Nelson & O'Connor (1964b) and shown diagramatically in figure 11.1 in Chapter 11 below, and calculated using equation 3.1;

$$\%Cr = \frac{I_{002} - I_{am}}{I_{002}} \times 100 \qquad \text{Equation 3.1}$$

where:-

I_{002} = the intensity of the 002 peak (the maximum between 21° and 23° 2 θ) in arbitrary units (figure 11.1)

I_{am} = the intensity of the amorphous background (the minima between 16° and 19° 2 θ) in the same arbitrary units (figure 11.1)

Compaction of size standardised granules was performed as described in section 2.2.8. Dried granules prepared using between 31.8 and 75.0 $\%^{w}/_{w}$ water inclusive in the wet mass were found to flow sufficiently well for tablets with acceptable weight uniformity to be prepared. However, dried granules prepared

using below 31.8 $\%^{w}/_{w}$ or above 75.0 $\%^{w}/_{w}$ water in the wet mass exhibited poor flow characteristics which was also apparent from their relatively high Hausner ratios and Carr's compressibility indices (table 3.2. and discussed in section 3.3.1). These samples required additional vibration of the feed shoe in a similar manner to that described for preparation of tablets from ungranulated MCC in section 2.2.8. in order to achieve satisfactory die filling and acceptable weight variation. The mechanical characteristics of the tablets produced was assessed by determining their tensile strength and work of failure as described in section 2.2.9.

3.3 Results and discussion

3.3.1 Effect of water concentration on the physical characteristics of granules

3.3.1.1 Bulk density

As the granulating water level was increased from 26.8 to 53.8 $\%^{w}/_{w}$ water in the wet mass, the poured and tapped bulk densities of size standardised dried granules increased (table 3.2). Staniforth et al (1988) also reported an increase in the poured and tapped bulk density of granules prepared from MCC and starch as the proportion of water in the wet mass was increased from an equivalent of 27.1 to 31.7 $\%^{w}/_{w}$. In the present study increasing the proportion of granulation fluid above 66.6 $\%^{w}/_{w}$ resulted in a decrease in the granule poured and tapped bulk densities (table 3.2). Furthermore, granules prepared from the highest levels of water, that is 80 and 83.3 $\%^{w}/_{w}$ water in the wet mass, yielded granules which had lower bulk densities than ungranulated MCC (table 3.2). The level of granulating water which would result in granules exhibiting the maximum poured and tapped bulk densities was estimated to be between approximately 50 and 55 $\%^{w}/_{w}$ in the original wet mass (figure 3.1).

It is recognised that accuracy and consistency of sieving as a technique for size separation is limited and will not provide perfect size standardisation (Allen, 1990). Nevertheless, since the size distribution of granules was standardised in the present study, it is considered that differences observed between the bulk densities of dried granules are less likely to arise from differences between their size distributions than from other physical differences. It is suggested that differences between the intraparticle porosity of different granulations and between the surface irregularity and thus interparticle porosity of products may be responsible for the observed differences in the bulk density of granules, discussed further in section 3.4 below.

Table 3.2. Method of preparation and particle characteristics of MCC granules prepared using varying proportions of water. (Data for ungranulated MCC discussed in section 2.3. has been included for comparison).

Mass of water added to 150g MCC powder (g)	Method notes (see below)	Concentration of water in wet mass before drying ($\%^{w}/_{w}$)	Bulk density (gcm^{-3})		Hausner ratio	Flow properties		Friability (%)
			Poured	Tapped		Carr's index	Flow class	
---	as received	-----	0.25	0.36	1.44	30.6	Poor	82
55	1,3	26.8	0.27	0.37	1.37	27.0	Poor	80
70	1,3	31.8	0.29	0.39	1.34	25.6	Poor	80
105	1,3	41.2	0.40	0.50	1.25	20.0	Fair	42
175	1,3,5	53.8	0.51	0.61	1.20	16.4	Good	14
300	1,3,5	66.6	0.37	0.45	1.22	17.8	Fair	14
450	1,3,4	75.0	0.29	0.36	1.24	19.4	Fair	20
600	1,3,4	80.0	0.20	0.26	1.30	23.1	Poor	60
750	1,3,4	83.3	0.20	0.27	1.35	25.9	Poor	69
600	1,6,3,4	65.0	0.30	0.37	1.23	18.9	Fair	13
600	2,7,3,4	80.0	0.20	0.26	1.30	23.1	Poor	62

1= wet granulation carried out using the technique described in section 3.2.1.

2 = wet granulation carried out using the technique described in section 3.2.1., modified as described in 3.2.4.

3 = drying carried out using the technique described in section 3.2.2.

4 = comminution carried out using an end runner mill as described in section 3.2.3.

5 = comminution carried out using a hammer mill as described in section 3.2.3.

6 = centrifugation of wet mass followed by drying of the concentrated solids without re-blending with the supernatant, as described in section 3.2.4.

7 = centrifugation of wet mass followed by re-blending of the concentrated solids with the supernatant, as described in section 3.2.4.

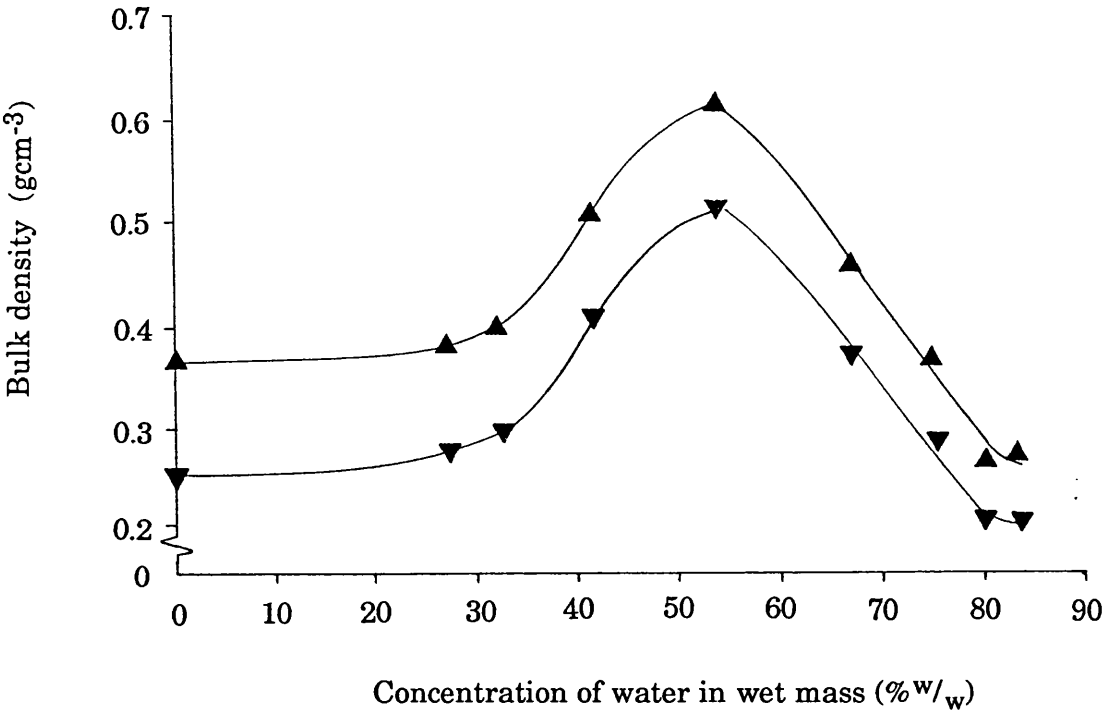


Figure 3.1 Relationship between the concentration of water in the wet mass and poured and tapped bulk densities for MCC powder and granules.
Key: Poured bulk density, ▼ . Tapped bulk density, ▲ .

3.3.1.2 Scanning electron microscopy

Qualitative examination of MCC powder and granules using scanning electron microscopy indicated that an increase in the amount of granulation fluid from 26.8 to 41.2 $\%^{w}/_{w}$ resulted in a progressive increase in the granule density and an increase in shape regularity (figure 3.2) . Micrographs presented by Staniforth et al (1988) also indicated an increase in MCC particle density following granulation with a solution of gelatinised starch, the density further increasing as the proportion of water in the wet mass was increased from an equivalent of 27.1 to 31.7 $\%^{w}/_{w}$. In the present study differences between the appearance of granules prepared from wet masses containing 41.2 and 53.8 $\%^{w}/_{w}$ water were less obvious, although granules prepared with 53.8 $\%^{w}/_{w}$ water may be described as exhibiting a slightly cracked surface structure (figure 3.2). The micrographs also suggested that increasing the proportion of granulation fluid above 53.8 $\%^{w}/_{w}$ resulted in a decrease in granule density and an increase in irregularity of the granule shape. Furthermore, granules dried from 66.6 and 75.0 $\%^{w}/_{w}$ water appeared to contain a greater degree of surface cracking in comparison with granules prepared from 53.8 $\%^{w}/_{w}$ water (figure 3.2). The emergence of surface cracks may be connected with the milling stage involved in the preparation of granules at the latter three levels of water. However, surface cracks were not apparent on milled dried granules prepared using more than 75.0 $\%^{w}/_{w}$ water (80.0 and 83.3$\%^{w}/_{w}$ water). Such granules had the appearance of irregular loose agglomerates of cellulose microcrystals and were similar in appearance to agglomerates of ungranulated MCC particles or granules prepared at the lowest water level (26.8 $\%^{w}/_{w}$ water in the wet mass). Possible reasons for the differences observed between granules using electron microscopy are discussed in section 3.4 below.

3.3.1.3 Porosity and pore size distribution

The pore size distribution of 125 to 180 μm particle size fractions of ungranulated MCC and for granules prepared from wet masses containing 41.2, 53.8 and 80.0 $\%^{w}/_{w}$ water are shown in figure 3.3. In addition, the intraparticle porosities (defined as described in section 2.2.4) are given in table 3.3 and shown graphically as a function of the proportion of granulating water in figure 3.4.

Figure 3.2 Scanning electron photomicrographs of ungranulated MCC and MCC granules prepared using different proportions of water and different treatments. (Note: column I shows a general view of groups of particles at a lower magnification, and column II shows details of individual agglomerates).

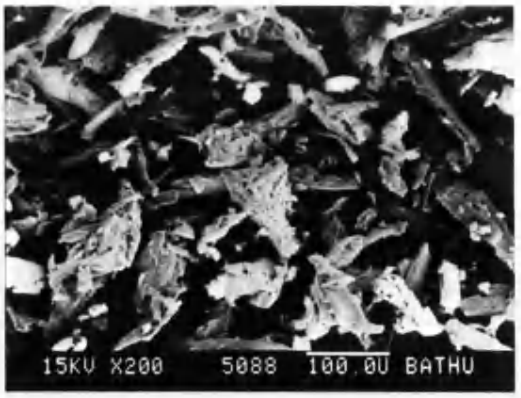
I II

a. Ungranulated MCC

b. Granules prepared with and dried from 26.8 $\%^{w}/_{w}$ water

c. Granules prepared with and dried from 31.8 $\%^{w}/_{w}$ water

d. Granules prepared with and dried from 41.2 $\%^{w}/_{w}$ water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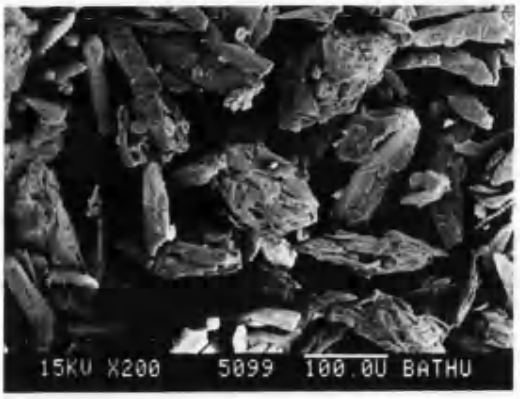
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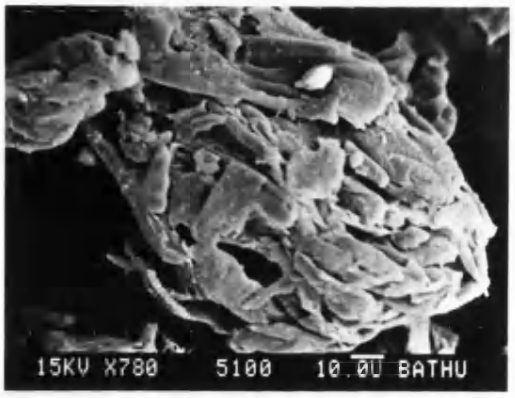
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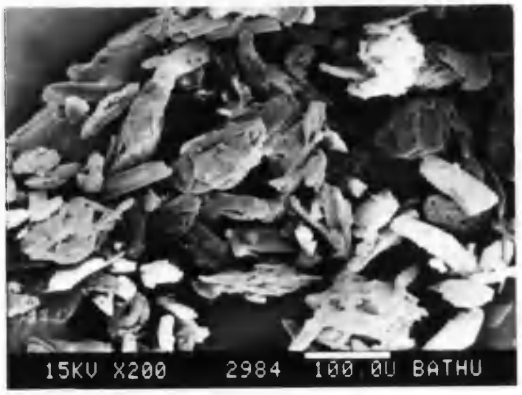
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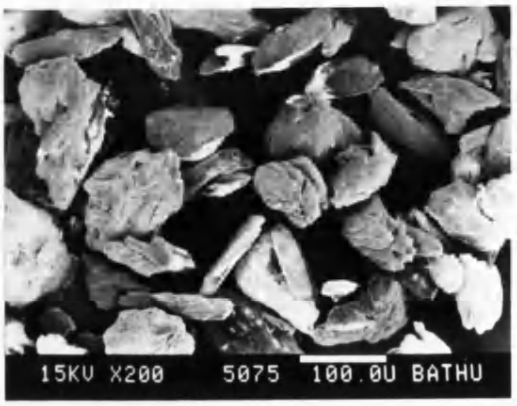
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15KV X780 5076 10.0U BATHU

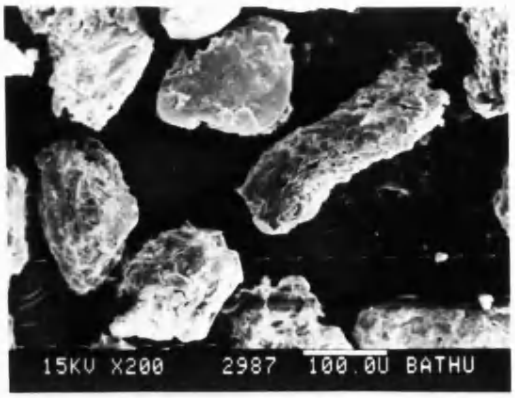
Figure 3.2 (continued)

I II

e. Granules prepared with and dried from 53.8 $\%^{w}/_{w}$ water

f. Granules prepared with and dried from 66.6 $\%^{w}/_{w}$ water

g. Granules prepared with and dried from 75.0 $\%^{w}/_{w}$ water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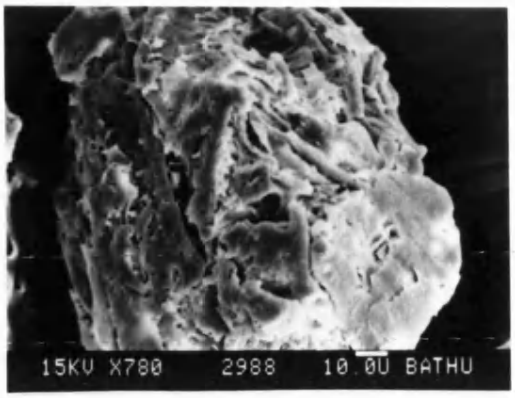
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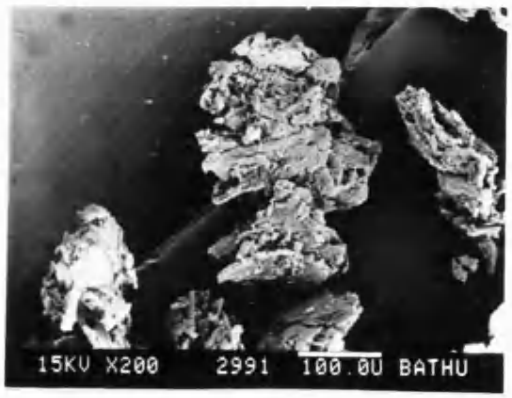
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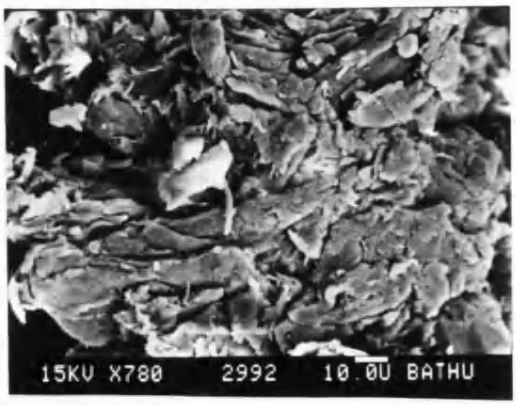
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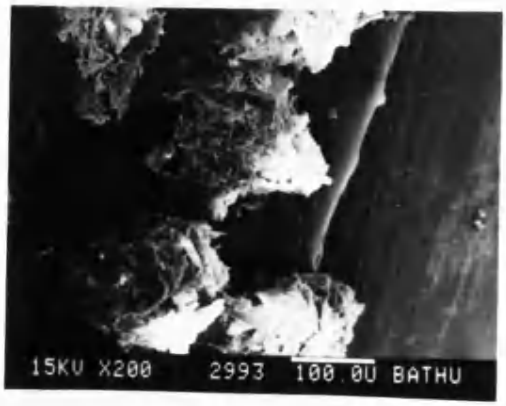
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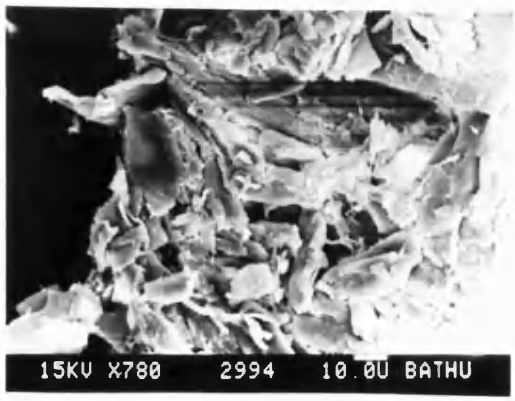

15KV X780 2994 10.0U BATHU

Figure 3.2 (continued)

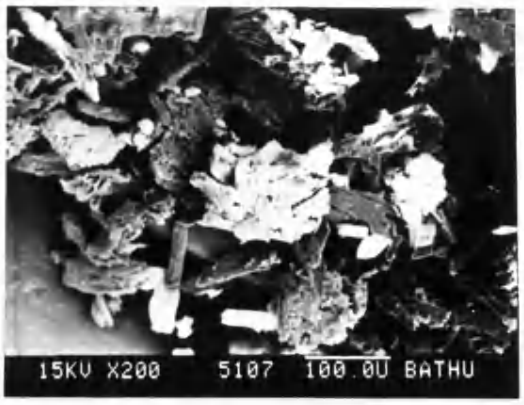
I II

h. Granules prepared with and dried from 80.0 $\%^{w}/_{w}$ water

i. Granules prepared with and dried from 83.3 $\%^{w}/_{w}$ water

j. Granules prepared with 80.0 $\%^{w}/_{w}$ water, centrifuged and dried from approximately 65 $\%^{w}/_{w}$ water in the wet mass

k. Granules prepared with 80.0 $\%^{w}/_{w}$ water, centrifuged and the supernatant readded before drying from 80 $\%^{w}/_{w}$ water in the wet mass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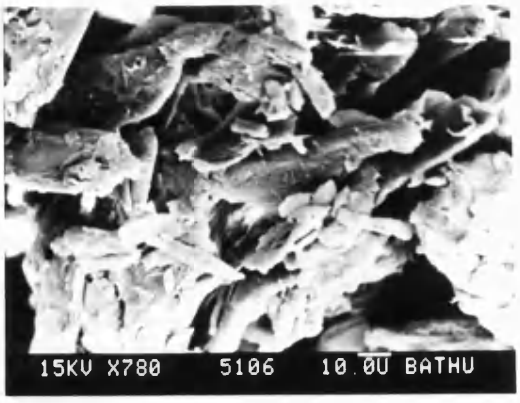
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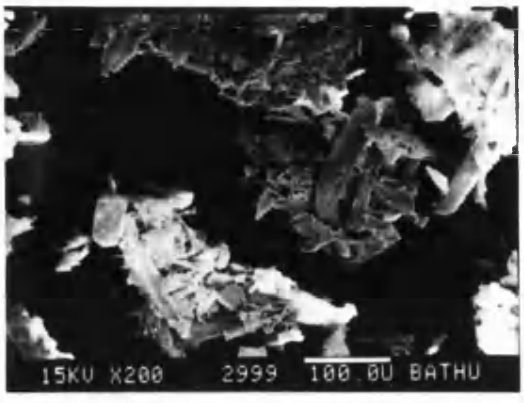
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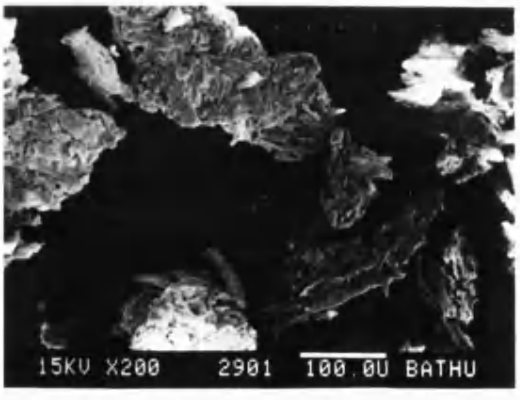
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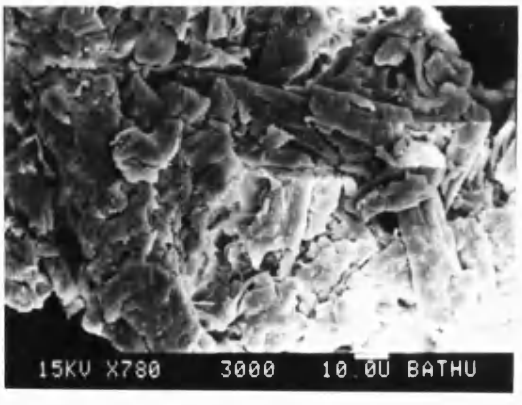
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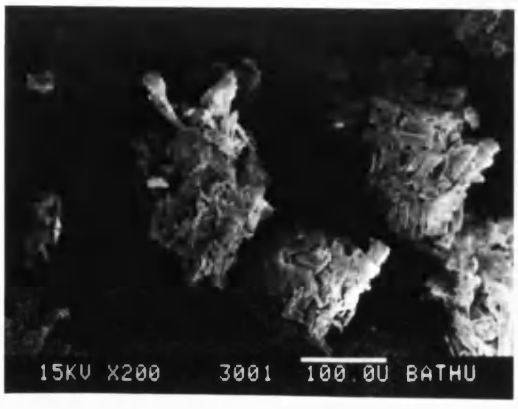
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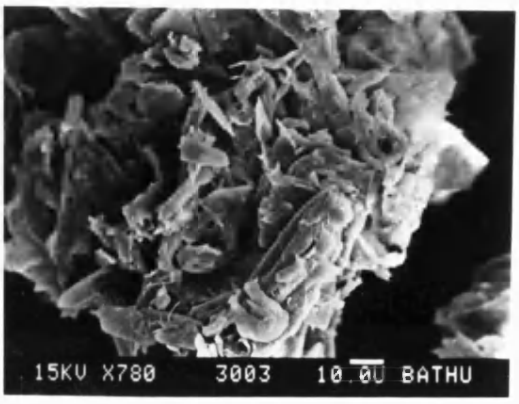
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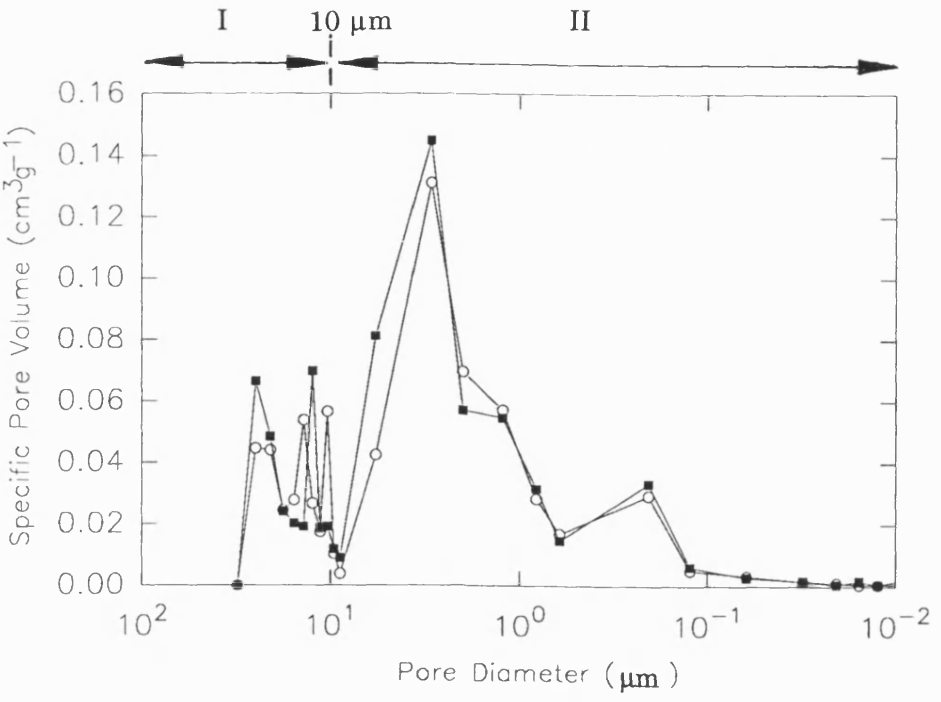
Figure 3.3 Pore size distributions of ungranulated MCC and granules prepared using varying proportions of water. Note: I is taken to be the interparticulate region, and II the intraparticulate region.

a. Duplicates of pore size distributions for ungranulated MCC.



b. Duplicates of pore size distributions for granules prepared using 41.2 $\%^{w}/_{w}$ water.

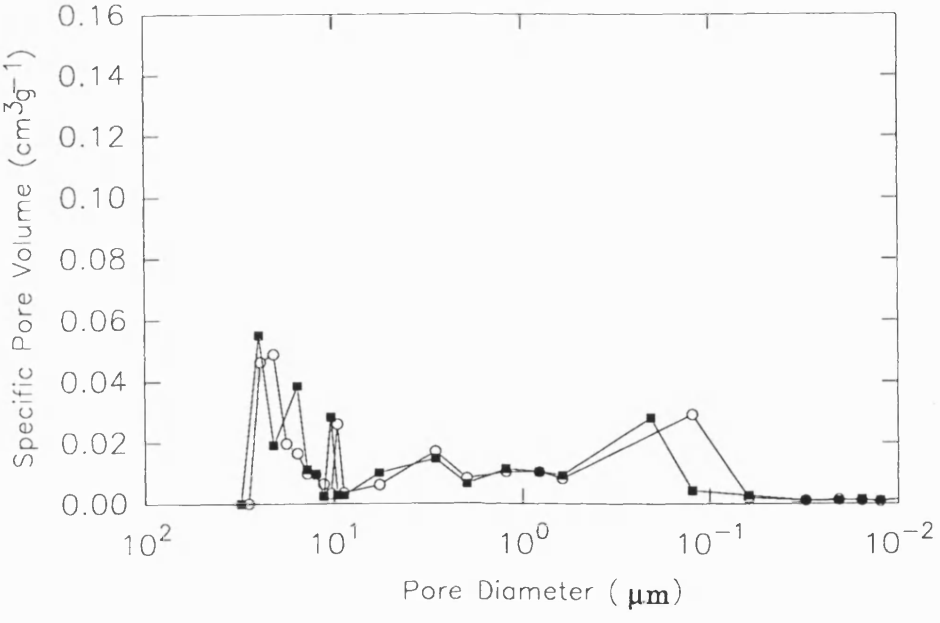
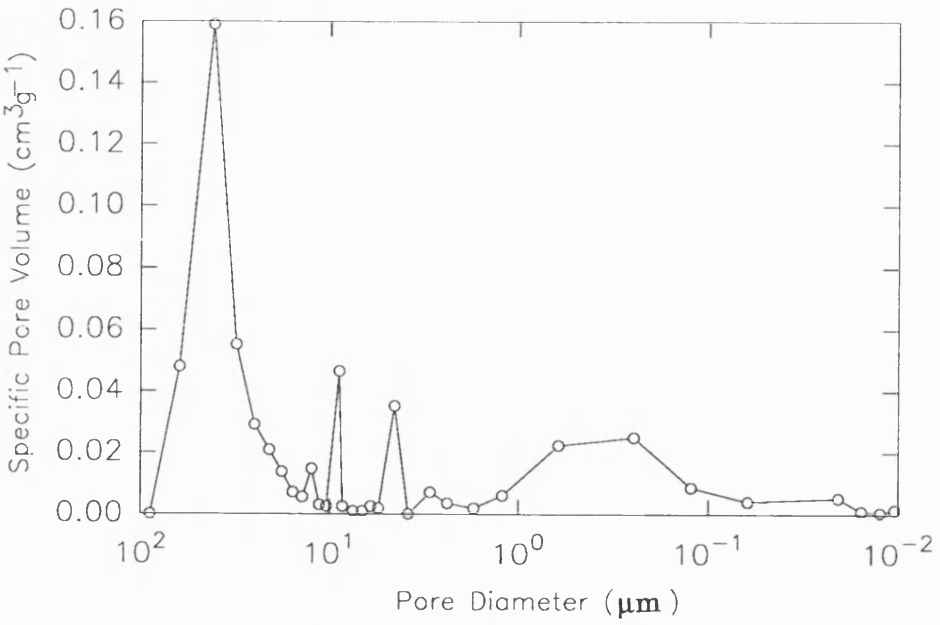


Figure 3.3 (continued)

c. Pore size distribution for granules prepared using 53.8 $\%^{w}/_{w}$ water.



d. Pore size distribution of granules prepared using 80.0 $\%^{w}/_{w}$ water.

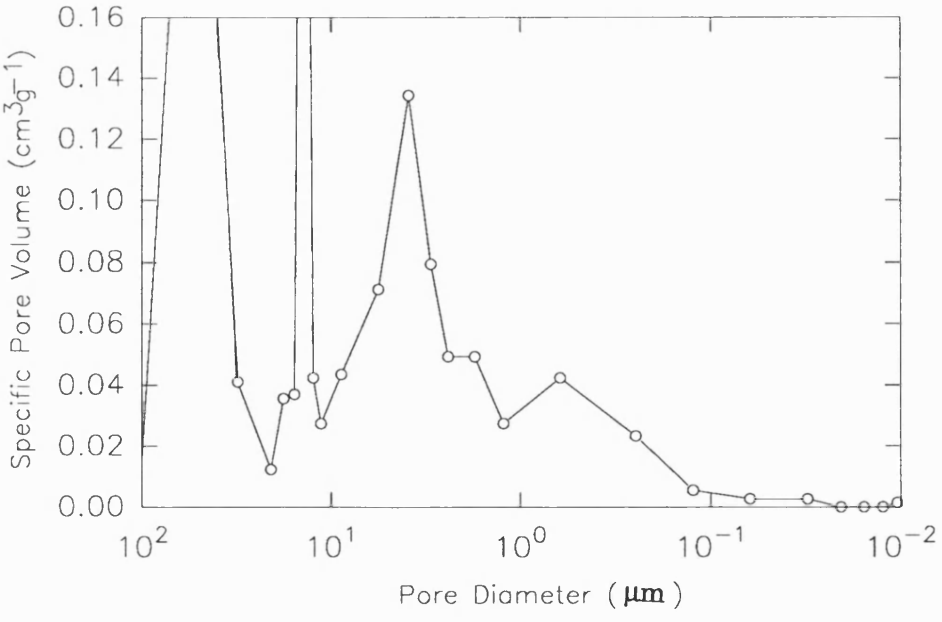


Table 3.3. Intraparticle porosity and specific surface area of ungranulated MCC and for granules prepared using varying proportions of water.

Proportion of water used to prepare the wet mass (for granules)	Total intraparticle porosity (cm^3g^{-1}) (values are for separate determinations)	Specific surface area (m^2g^{-1}) (values are for separate determinations)
Ungranulated MCC	0.42, 0.48	1.29, 1.28
Granules, 41.2 $\%^w/_w$	0.08, 0.11	0.41, 0.40
Granules, 53.8 $\%^w/_w$	0.09	0.76
Granules, 80.0 $\%^w/_w$	0.51	1.41

The porosimetry data was considered to be reasonably reproducible for repeat determinations for both ungranulated MCC and for granules prepared with 41.2$\%^w/_w$ water (figure 3.3 and table 3.3). Granulation with 41.2 $\%^w/_w$ water resulted in a reduction in both the inter- (figure 3.3) and intragranular porosity (figure 3.3 and table 3.3.) in comparison with ungranulated MCC. Granules prepared from 53.8 $\%^w/_w$ water exhibited a broadly similar intragranular porosity and pore size distribution in comparison with granules prepared with 41.2 $\%^w/_w$ water (figures 3.3 and 3.4, and table 3.3.). However, only limited macropore analysis of mercury intrusion data was carried out for ungranulated MCC and for granules prepared with 41.2 $\%^w/_w$ water and this prevented comparison with the intergranule porosity of granules prepared with 53.8 $\%^w/_w$ water (figure 3.3). There was a relatively high number of pores with an approximate diameter of 0.4 μm in ungranulated MCC and granules prepared from 41.2 and 53.8 $\%^w/_w$ (figure 3.3), suggesting that pores of this size in the original ungranulated MCC were largely retained on granulation with these amounts of water. Increasing the level of granulating water to 80.0 $\%^w/_w$ (figure 3.3) resulted in a substantial increase in the intergranular porosity in comparison with granules prepared from lower amounts of water (figure 3.3). The intragranular porosity and pore size distribution of granules prepared with 80.0 $\%^w/_w$ water was similar to that for ungranulated MCC shown qualitatively in figure 3.3, and quantitatively in table 3.3 and figure 3.4. Both ungranulated MCC and granules prepared using 80.0 $\%^w/_w$ water consisted of particles which contained a large number of pores with a diameter of approximately 4 μm which were absent from particles granulated using 41.2 and 53.8 $\%^w/_w$ water (figure 3.3). Due to insufficient data, the level of granulating water which would result in granules exhibiting the minimum

intragranular porosity, the latter property considered an indicator of intragranular bonding, could not be estimated with a high degree of certainty. However, interpolation of the results suggested minimum intragranular porosity would occur with the addition of approximately 40 - 60 %^{w}/w water in the original wet mass (figure 3.4).

A decrease in intragranular porosity with increasing amount of granulation fluid has been reported by other workers for a wide variety of materials other than MCC (e.g. Jaegerskou et al, 1984; Tapper & Lindberg, 1986). The increase in granule porosity observed in the present study with high granulation fluid levels has not been reported previously for granules containing MCC. However, Hunter & Ganderton (1973) reported that increasing the proportion of water used to prepare calcium phosphate granules resulted in a slight increase in granule porosity, albeit only that resulting from the largest pores as determined by mercury pycnometry. These workers suggested that at higher water levels, an increase in wet granule cohesion coupled with particle interlocking prevented particles within granules from assuming closer packing during agitation. Although such behaviour may contribute to the increase in granule porosity and reduction in granule density observed at the high granulation fluid levels in the present study, it is considered unlikely that the explanation proposed by Hunter & Ganderton (1973) satisfactorily accounts for the the large differences between granule porosity and density reported here. In a study of granules prepared from lactose using increasing amounts of water, Wikberg & Alderborn (1990) found a different effect from that reported by Hunter & Ganderton (1973). In this case an initial decrease was followed by an increase in porosity. These workers suggested that the increase in porosity observed at higher granulation fluid levels was due to reduced densification during wet screening (Wikberg & Alderborn, 1990). However, in the present study, granules prepared using proportions of water in excess of or equal to 53.8 %$^{w}/_{w}$ were not wet screened before drying, and granules prepared using a lower amount of water gently passed through a screen before drying. Thus, it was considered unlikely that differences between granule types with respect to granule porosity determined quantitatively by mercury porosimetry and qualitatively from electron micrographs as discussed above were due to the variable effects of wet screening. Possible reasons for the variable effect of granulation fluid level on the inter- and intragranular porosity of dried granules reported in the present study are discussed in section 3.4 below.

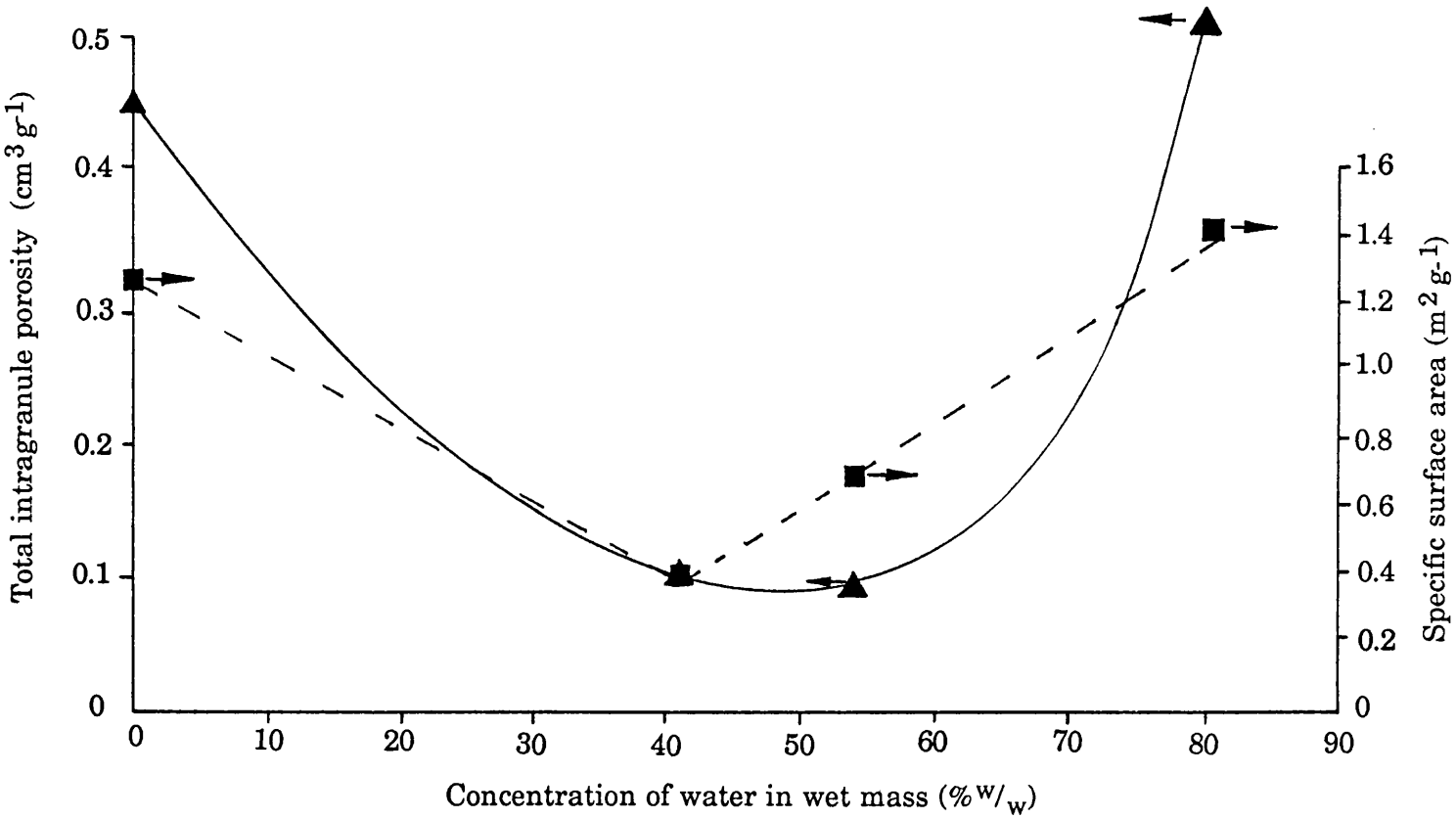


Figure 3.4 Relationship between the concentration of water in the wet mass and both intragranule porosity ▲, and specific surface area ■ . Note: Data for ungranulated MCC is included for comparison.

3.3.1.4 Specific surface area

Granule preparation using 41.2 $\%^{w}/_{w}$ water resulted in an approximately three-fold decrease in the specific surface area determined by nitrogen adsorption in comparison with ungranulated material (table 3.3). It was considered unlikely that the decrease in surface area resulting from granulation at the 41.2 $\%^{w}/_{w}$ water level was solely due to the increase in mean particle size from approximately 60 μm for the unsized ungranulated material (section 2.3.1) to between 90 and 180 μm for size standardised granules. This is because the specific surface area of particles of ungranulated MCC with diameters ranging from 75 - 90 μm obtained using method C (section 2.2.3) was similar to that for unsized material (section 2.3.3) and further because the differences in specific surface area were consistent with the appearance of particles (figures 3.2a and 3.2d).

Preparation of granules using 53.8 $\%^{w}/_{w}$ water in the wet mass yielded granules which had a a higher surface area, although similar intragranular porosity as determined by mercury intrusion, in comparison with granules prepared from 41.2 $\%^{w}/_{w}$ water (table 3.3 and figure 3.4). Differences between relative intraparticle porosity and relative specific surface area values obtained for granules prepared from 41.2 and 53.8 $\%^{w}/_{w}$ water may in part be attributable to differences between the size fractions used for the two studies. However, this is considered to be an incomplete explanation since specific surface areas using nitrogen adsorption were carried out using size standardised granules recombined according to the formula shown in table 3.1, whereas mercury porosimetry was performed on 125 to 180 μm size fractions, the mean particle sizes being similar. By consideration of the electron micrographs of granules (figure 3.2) it is suggested that granules prepared using 53.8 $\%^{w}/_{w}$ water had a higher number of pores which were inaccessible to mercury penetration although accessible to nitrogen molecules in comparison with granules prepared with 41.2 $\%^{w}/_{w}$ water.

Increasing the proportion of water used during wet massing to 80.0 $\%^{w}/_{w}$ resulted in a further increase in specific surface area to a value greater than that for the original ungranulated material (table 3.3). This was considered consistent with particles prepared from 80.0 $\%^{w}/_{w}$ water having a high intragranular porosity (table 3.3) although with a different particle size distribution to that of the ungranulated MCC sample. Granule specific surface area, which may also be considered as an indicator of the degree of intragranular and intraparticle bonding,

was found to pass through a minimum for granules prepared with approximately 40 $\%^{w}/_{w}$ water (figure 3.4). This estimated minimum does not correspond with the proportion of added water which yielded granules exhibiting the highest poured and tapped bulk densities which was between approximately 50 and 55 $\%^{w}/_{w}$ in the original wet mass (figure 3.1). This suggests that intergranular associations as indicated by bulk density changes were influenced differently and varied independently of intragranule structural changes.

3.3.1.5 Friability

The friability of granules initially decreased with increasing water level used for wet granulation (table 3.2) and then increased. Minimum friability would have been obtained by granulating with between 53.8 and 66.6 $\%^{w}/_{w}$ water (figure 3.5). Remon & Schwartz (1987) reported that for granules prepared from lactose and MCC in the proportions 75:25, an increase in the granulation fluid level equivalent to the range 26 to 31 $\%^{w}/_{w}$ water in the wet mass resulted in a decrease in granule friability. This was suggested to result from incomplete granulation at the lower fluid level. A reduction in granule friability was observed between these levels of granulating fluid in the absence of dissolved solids in the present study. However, in the present study increasing the proportion of water during wet massing above 66.6 $\%^{w}/_{w}$ resulted in an increase in granule friability (table 3.2 and figure 3.5). Although there was no conclusive difference between the mercury intrusion intragranular porosity for granules prepared using 41.2 and 53.8 $\%^{w}/_{w}$ water (table 3.3), granules prepared using 53.8 $\%^{w}/_{w}$ water had a lower friability than granules prepared with 41.2 $\%^{w}/_{w}$ (figure 3.5) water but a higher specific surface area (figure 3.4). Granules possessing a high specific surface area may be expected to be more susceptible to fragmentation, and granules exhibiting similar intragranular porosity, similar friabilities. However, the results of the present study suggest that the ability of granules to withstand attrition is not necessarily related to the degree of bonding within the bulk particles as assessed by granule surface area from nitrogen adsorption or by porosity from mercury intrusion studies.

It is suggested here that the presence of easily removable particles on the surface of granules prepared using 41.2 $\%^{w}/_{w}$ water results in a higher granule friability in comparison with granules prepared from 53.8 $\%^{w}/_{w}$ water since the latter may be expected to be more completely wetted during granulation and therefore exhibit a higher degree of densification during drying. However,

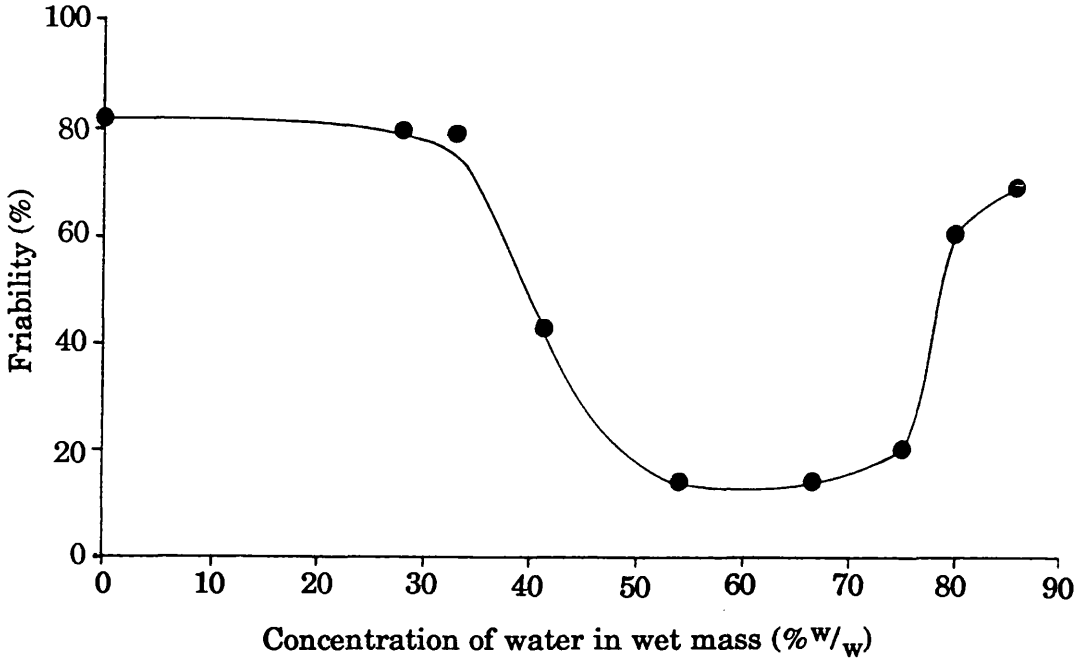


Figure 3.5 Relationship between the concentration of water in the wet mass and the friability of MCC granules. Note: Data for ungranulated MCC is included for comparison.

porosimetry data suggest that the presence or absence of such easily removable particles on the granule surface had no effect on intragranular porosity. The observed increase in granule specific surface area with a reduction in granule friability as the amount of water used to prepare granules was increased form 41.2 to 53.8 $\%^{w}/_{w}$ may be due to granule milling influencing deep intraparticle bonding to a greater extent than particle surface bonding. However, it is considered more likely that a higher degree of bonding on the granule surface produced in samples prepared using increased water levels occurred as an indirect result of longer exposure of MCC to water during granule drying, which provided a greater opportunity for densification and increased interparticulate contacts between surfaces (section 3.4.1), thereby reducing granule friability without reducing granule surface area. Wikberg & Alderborn (1990) have also reported that the friability and porosity of granules prepared from lactose are not necessarily related, and they suggested that a gradient in strength properties occurred across individual granules.

3.3.1.6 Degree of crystallinity

Extensive milling has been widely reported to reduce the degree of crystallinity of cellulose (e.g. Nelson & O'Connor,1964a; Nakai et al, 1977a). The percentage crystalline material in granules prepared using 41.2 $\%^{w}/_{w}$ water and not milled was similar to that for granules prepared using higher amounts of water and milled either using an end runner mill or a hammer mill (table 3.4). Thus, the short milling times used did not appear to significantly reduce the degree of crystallinity of cellulose, a finding anticipated from the results presented by Nelson & O'Connor (1964a).

Table 3.4 Percentage of crystalline material in various MCC granules types

Method notes (key as table 3.2)	Concentration of water in wet mass before drying ($\%^{w}/_{w}$)	Percentage crystalline material (*%Cr*)
1, 3	41.2	86
1, 3, 5	53.8	85
1, 3, 5	66.6	85
1, 3, 4	80.0	87
1, 6, 3, 4	65.0	87

3.3.2 Effect of proportion of granulating fluid on granule compactibility

From the profiles for tablet strength (figures 3.6.a and 3.7.a) and work of failure (figures 3.6.b and 3.7.b) as a function of compaction force it can be seen that granule compactibility varied with the level of water used during wet massing. The relationships between the water concentration in the wet masses with the strength and toughness of tablets prepared at 15 kN are shown in figure 3.8. With the exception of granules prepared from 80.0 and 83.3 $\%^{w}/_{w}$ water, all granules exhibited inferior compactibility in comparison with ungranulated material (figures 3.6, 3.7 and 3.8). At the two highest water levels, granules exhibited comparable compactibility to ungranulated MCC (figures 3.7 and 3.8). The compactibility of wet granulated MCC decreased with an increase in the water level between 26.8 and 41.2 $\%^{w}/_{w}$ (figures 3.6 and 3.8). Thereafter, an increase in the level of granulation fluid resulted in an improvement in granule compactibility (figures 3.7 and 3.8). The granulation water level resulting in minimum compactibility occurred was approximately 40 $\%^{w}/_{w}$ (figure 3.8) which was less than the water level at which both the maximum for bulk density (table 3.2 and figure 3.1) and the minimum for friability occurred (table 3.2 and figure 3.5). This supports the theory, outlined in section 3.3.1 above, that the surface characteristics manifested in bulk properties may vary independently of and be different from internal structural characteristics. This interpretation appears to be further supported by consideration of the similarity between the concentration of water yielding minimum compactibility and that expected to yield minimum granule specific surface area (figures 3.4 and 3.8). Although insufficient data precluded accurate determination of the water level which would result in minimum intragranule porosity, the present results suggest that this water level may not coincide with that resulting in minimum granule compactibility (figures 3.4 and 3.8). However, the approximate correlation observed between internal structural changes and the mechanical properties of tablets produced suggests that granule deformability increased with a reduction in intraparticle bonding in the uncompressed granule. Krycer et al (1982a) also suggested that for a wide variety of materials (which did not include cellulose or MCC), increased intragranule porosity and granule friability in general results in increased granule compactibility through an increase in interparticulate friction and an increase in the ability of granules to deform upon application of an applied stress.

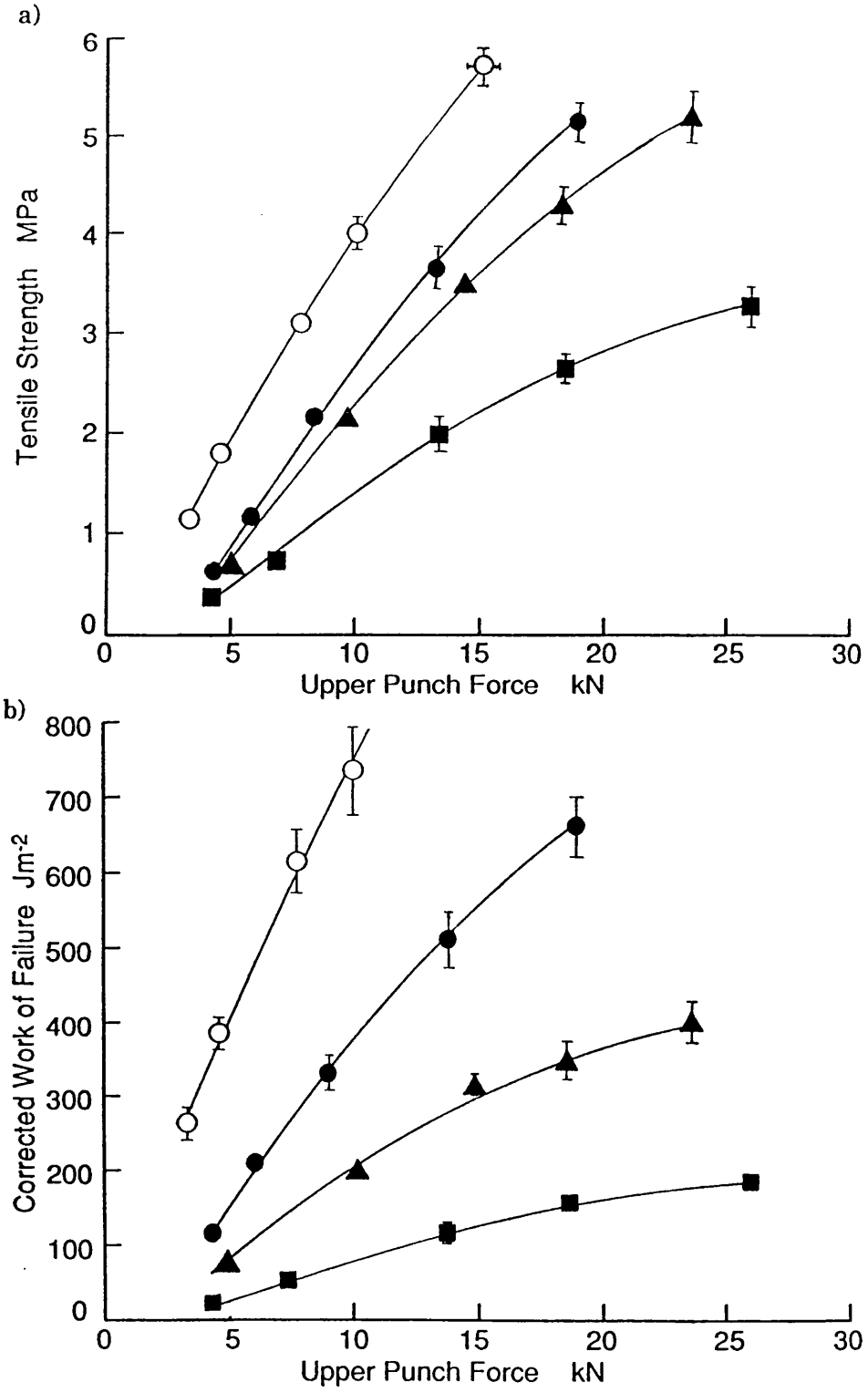


Figure 3.6 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets produced from granules prepared and dried from varying levels of water below or equal to 41.2 $\%^{w}/_{w}$.
Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: ○
Granules prepared with and dried from; i) 26.8 $\%^{w}/_{w}$ water: ●
ii) 31.8 $\%^{w}/_{w}$ water: ▲ iii) 41.2 $\%^{w}/_{w}$ water: ■

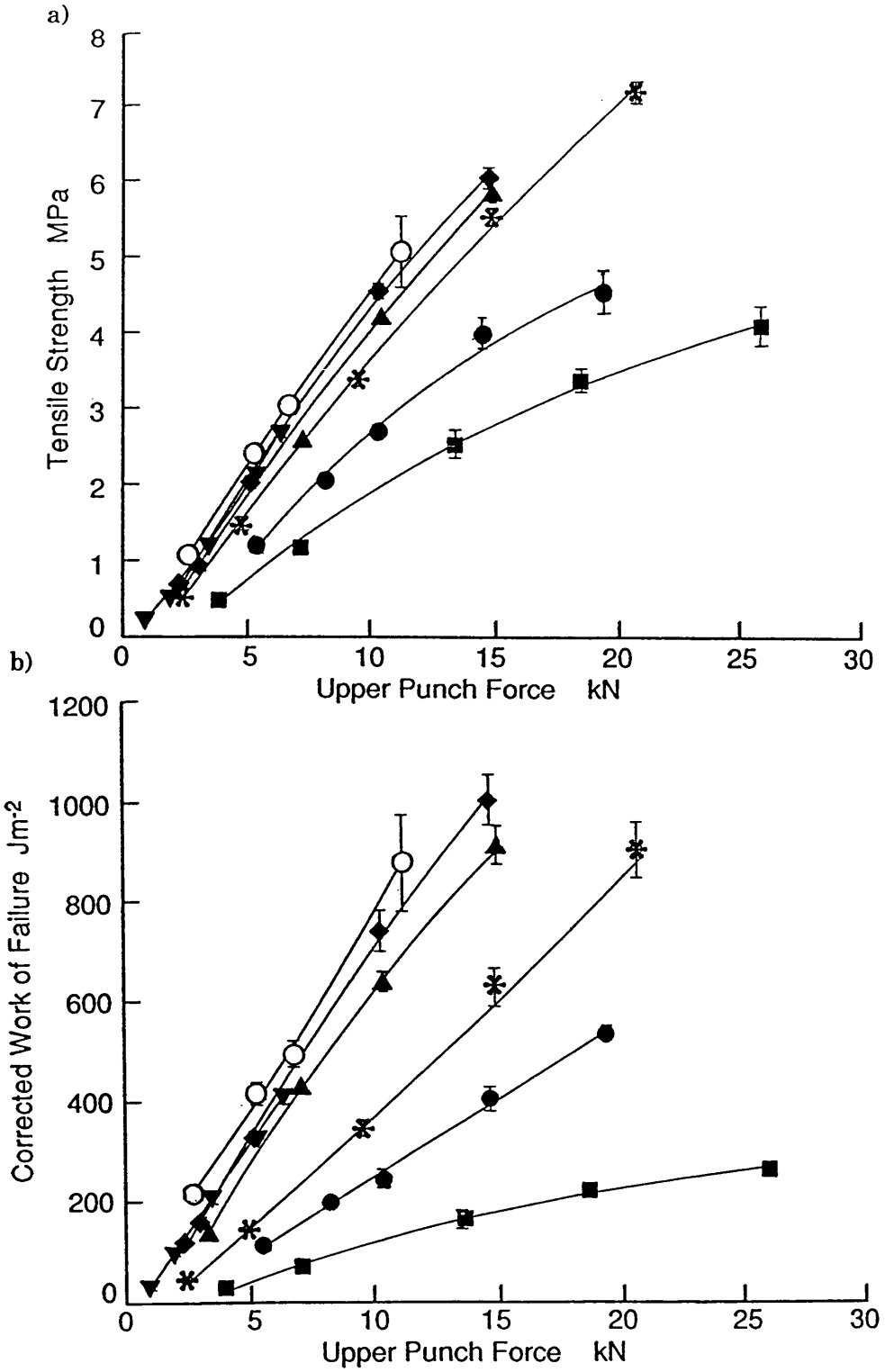


Figure 3.7 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets produced from granules prepared and dried from varying levels of water above or equal to 41.2 $\%^{w}/_{w}$.

Note: Error bars represent 95% confidence limits.

Key: Ungranulated MCC: ○

Granules prepared with and dried from; i) 41.2 $\%^{w}/_{w}$ water: ■ ii) 53.8 $\%^{w}/_{w}$ water: ● iii) 66.6 $\%^{w}/_{w}$ water: ✻ iv) 75.0 $\%^{w}/_{w}$ water: ▲ v) 80.0 $\%^{w}/_{w}$ water: ◆ vi) 83.3 $\%^{w}/_{w}$ water: ▼

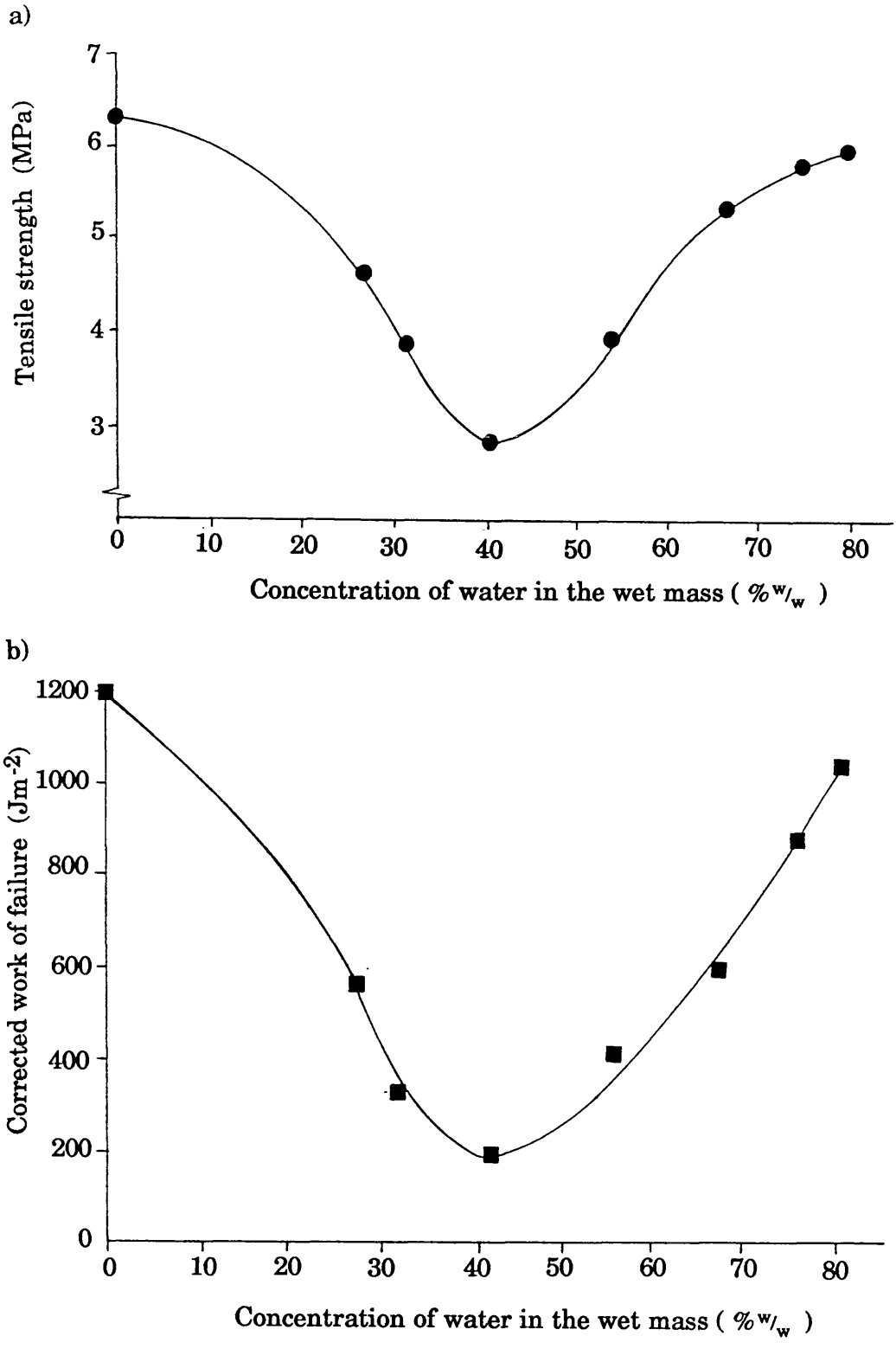


Figure 3.8 Relationship between the proportion of water used to granulate MCC and a) tensile strength, and b) corrected work of failure, of tablets produced using an upper punch force of 15kN.
Key: Tablet tensile strength; ● Tablet corrected work of failure; ■

Malinowski & Smith (1974) reported that for tablets prepared from spheronised MCC and paracetamol in the ratios 4:1, an increase in the water level used for wet massing from 20 to 25 $\%^{w}/_{w}$ resulted in a reduction in tablet strength. However, reasons for the reduction in compactibility were not proposed. Staniforth et al (1988) reported a decrease in granule compactibility and an increase in particle density as the amount of granulation fluid, which contained gelatinised starch, used to granulate MCC was increased from the equivalent of 27.1 to 31.7 $\%^{w}/_{w}$ water in the wet granules. Similar effects have been reported in the present study using equivalent amounts of granulating fluid. The progressive reduction in compactibility and increase in granule densification of MCC following wet granulation with increasing proportions of water was attributed to a progressive reduction in the ability of the material to undergo plastic deformation (Staniforth et al, 1988) although such differences were not quantifiable from creep studies (Staniforth et al, 1987). A reduction in the deformability of particles would be expected to result in a reduced area of interparticulate contact on compaction and consequently a reduced interparticulate bonding within compacts as discussed by Staniforth et al (1988). However, reasons for the formation of dense granules following wet granulation were not proposed by the latter authors. Nor do the results of Staniforth et al (1988) anticipate the increase in granule porosity and surface area together with the improvement in compactibility when the proportion of the water in the wet mass was increased above 41.2 $\%^{w}/_{w}$ found in the present study.

Alderborn & Nyström (1982a) and Wong et al (1988) reported that the strength of tablets produced from plastically deforming materials was influenced by the particle shape and surface roughness, with irregular particles resulting in stronger tablets than regular particles. An increase in the irregularity of the particle shape may enable increased interparticulate contact upon compaction (Alderborn & Nyström, 1982a; Wong et al, 1988). By comparison, the strength of tablets produced from materials consolidating principally by fragmentation was reported to exhibit little dependence on particle shape (Alderborn & Nyström, 1982a; Wong et al, 1988). This was attributed to the deformation mechanism negating any influence due to the original particle shape and roughness on subsequent interparticulate contact area (Alderborn & Nyström, 1982a; Wong et al, 1988). Ungranulated MCC has been reported to consolidate principally by plastic deformation (e.g. David & Augsberger, 1977). Hence, differences observed

in the present study between the compactibility of differently prepared granules could, in part, result from particle shape changes. However, differences in particle shape between granules prepared in the present study were considered small and thus unlikely to be a major reason for the large differences in compactibility observed for granules prepared from different concentrations of water in the present study.

3.4 Theoretical considerations

Particles of ungranulated MCC are aggregates of microcrystals formed by spray drying (section 1.5.2). During addition of water, formation of liquid bridges between the solid particles results in particle cohesion and hence wet agglomeration as discussed in section 1.1.2.1. Further, since water is capable of penetrating the non-crystalline regions of cellulose / MCC by disrupting intermolecular hydrogen bonds (section 1.3.1.5), increased internal as well as external wetting of the primary MCC particles can be expected until the amount of water added results in granules reaching the capillary stage. Addition of further amounts of water results in granule overwetting and the appearance of continuous surface water.

3.4.1 Proposed mechanism for the effect of increasing granulation water levels up to approximately 40 $\%^{w}/_{w}$ on granule physico-mechanical characteristics - Type I MCC granules

It has been reported by other workers (Alleva & Schwartz, 1986; Rowe & Sadeghnejad, 1987; Hancock et al, 1991) that in the case of Avicel PH-101 wet massed with water, maximum cohesion within the granule bed, taken to indicate attainment of the capillary state, was observed when the amount of water in the wet mass was between approximately 53 and 67 $\%^{w}/_{w}$. As discussed in section 1.5.5.1, the lower value of 17 to 23 $\%^{w}/_{w}$ water in the wet mass which was suggested by Staniforth et al (1988) and Heng & Staniforth (1988) to result in maximum wet mass cohesion may be due to differences between the methodologies. It is possible that the use of higher shear during granulation as in the present study results in the continuous surface film of moisture at a water level greater than 23.1 $\%^{w}/_{w}$.

In the present study as the weight of granulation fluid was increased, the porosity, surface area, friability and compactibility of MCC granules passed

through a minimum over the range 40 to 70 $\%^{w}/_{w}$, (figures 3.4, 3.5 and 3.8) and by interpolation, bulk density was estimated to pass through a maximum between 50 and 55 $\%^{w}/_{w}$ water in the wet mass (figure 3.1). Thus, the minimum and maximum for the physico-mechanical characteristics of MCC granules found in the present study approximately coincide with the proportion of water reported by Alleva & Schwartz (1986), Rowe & Sadeghnejad (1987) and Hancock et al (1991) required to achieve maximum cohesiveness of the wet granule bed and presumed concomitant with attainment of the capillary state. Applying these relationships to interpret the results of the present study suggests that as the water in the wet mass was increased up to the approximate capillary state, an increase in wet intragranular binding would be anticipated. As water is evaporated from the wet MCC granules and menisci are formed between microcrystals, it is proposed here that the surface tension of the water within wetted granules may result in adjacent microcrystals being drawn close enough together to allow intraparticulate bonding, perhaps by hydrogen bonding. The increase in intermicrocrystal contact area results in a reduction in granule porosity and surface area in comparison with the original ungranulated material. In addition, the surface tension forces act to reduce the irregularity of the particle shape, since the trend towards minimum surface free energy promotes smoothing and spheronisation. Both effects would tend to result in an increase in granule bulk density. Thus the effect of the amount of granulating water on the granule porosity (table 3.3), pore size distribution (figure 3.3) and surface area (table 3.3) was broadly consistent with the differences in bulk density and particle appearance as discussed above (table 3.2 and figure 3.1), with a reduction in inter- and intraparticle porosity generally associated with increased bulk density and reduced particle rugosity. Further, as discussed in section 3.3.1, the absence of co-attainment of minima and maxima for different MCC granule properties found in the present study indicates that the relationship between granule properties and degree of wet binding is almost certainly more complex than that envisaged in the simple model outlined above. However, once the particles are completely engulfed by water, particle surfaces become separated by a continuous surface film of water which further alters the subsequent properties as discussed in section 3.4.3. below. In addition, since a dissolved binder was not included in the formulations used in the present study, any alterations in the physico-mechanical characteristics of granules found using different moisture levels to prepare wet masses were assumed to be directly due to a complex interaction between water and MCC at different concentrations.

Van der Zwan & Siskens (1982) inter alia have suggested that a number of processes are involved in the volume reduction of a granulation during compaction. In addition to rearrangement, deformation and fragmentation of the granules themselves, rearrangement, deformation and fragmentation of the primary particles within the granules also occurs. Thus, increased intraparticulate bonding would also be expected to reduce the ability of particles to deform under an applied load. Consequently, on compaction, fewer interparticle bonds would be formed resulting in the formation of weaker, less tough tablets.

The theory developed above to account for the effect of wet granulation on the physico-mechanical characteristics of MCC is similar to the theory of hornification proposed by other workers to explain the effect of removal of water from cellulose fibres on fibre deformability and wet plasticity, and for the reduction in paper strength resulting from pre-drying of cellulose pulp (section 1.4.2). These workers also related physical changes in the product to physical changes in cellulose as the result of increased intrafibre hydrogen bonding which was termed hornification, and was similarly accompanied by a reduction in the specific surface area of the cellulose pulp as determined by nitrogen adsorption. However, the theory of increased intraparticulate bonding being promoted by wet granulation in addition to the mechanisms proposed above by which granules are densified in the absence of dissolved binders warrants further experimental examination.

3.4.2 Effect of partial dewatering of MCC slurries by centrifugation

It was considered that differences in performance of MCC granules may be at least partly dependent on the relative influence of water present during granulation and that present during drying. For this reason, samples of wet mass containing 80.0 $\%^{w}/_{w}$ water were centrifuged to provide a concentration of approximately 65 $\%^{w}/_{w}$ water in the wet mass following centrifugation. To assess the additional potential effect of the centrifugation stage on MCC granule performance, a 'control' wet mass was prepared with a similar level of water which was then centrifuged and the supernatant re-added to the slurry before drying.

Comparison of the bulk density (table 3.2), friability (table 3.2), appearance (figures 3.3j and 3.3k) and compactibility (figure 3.9) of granules

prepared from wet masses containing 80.0 $\%^{w}/_{w}$ water and subsequently dried with and without centrifuging reveals that the centrifuging process alone has little effect on the physico-mechanical characteristics of wet massed MCC, and more specifically does not appear to promote intragranular bonding by exerting pressure on the microcrystals. The compaction profiles (figure 3.9) and bulk density data (table 3.2) for granules prepared from a wet mass containing 80.0 $\%^{w}/_{w}$ water centrifuged to 65 $\%^{w}/_{w}$ solids prior to drying were between those obtained for granules prepared and dried from 66.6 and 80.0 $\%^{w}/_{w}$ water level. This suggests that both the presence of water during wet massing, and its presence during drying has an effect on compactibility and bulk density. More specifically, the presence of additional water during the granulation phase results in an improvement in dried granule compactibility, and a reduction in the wet mass water content before commencing convective drying has a detrimental effect on dried granule compactibility at the latter granulation water levels. However, granule friability appears to be related to the proportion of water present during the drying stage rather than the level of water during wet massing (table 3.2). In addition, the appearance of centrifuged granules is similar to that for granules prepared from 66.6 $\%^{w}/_{w}$ water (figure 3.2), suggesting that granule density is related to the proportion of water present in the wet mass before drying rather than to the proportion of water present during wet massing.

3.4.3 Proposed mechanism for the effect of increasing granulation water levels greater than approximately 40 $\%^{w}/_{w}$ on granule physico-mechanical characteristics - Type II MCC granules

Specific surface area data (table 3.3) suggested that wet massing with levels of water greater than 40 - 45% resulted in granules with progressively increased internal surfaces, perhaps accounting for the increased ability to deform during compaction. The increased internal surface area, and accompanying improvement in compactibility, together with the increase in irregularity of the granule shape (figure 3.2) which occurred as the result of addition of increased levels of granulation fluid to the MCC wet mass has not been demonstrated or discussed previously by other workers. However, Hunter & Ganderton (1973) have reported a similar although less pronounced effect in the case of granulation of calcium phosphate where an increase in volume of water added above 150 $\%^{v}/_{v}$ resulted in a slight increase in granule porosity and decrease in granule crushing

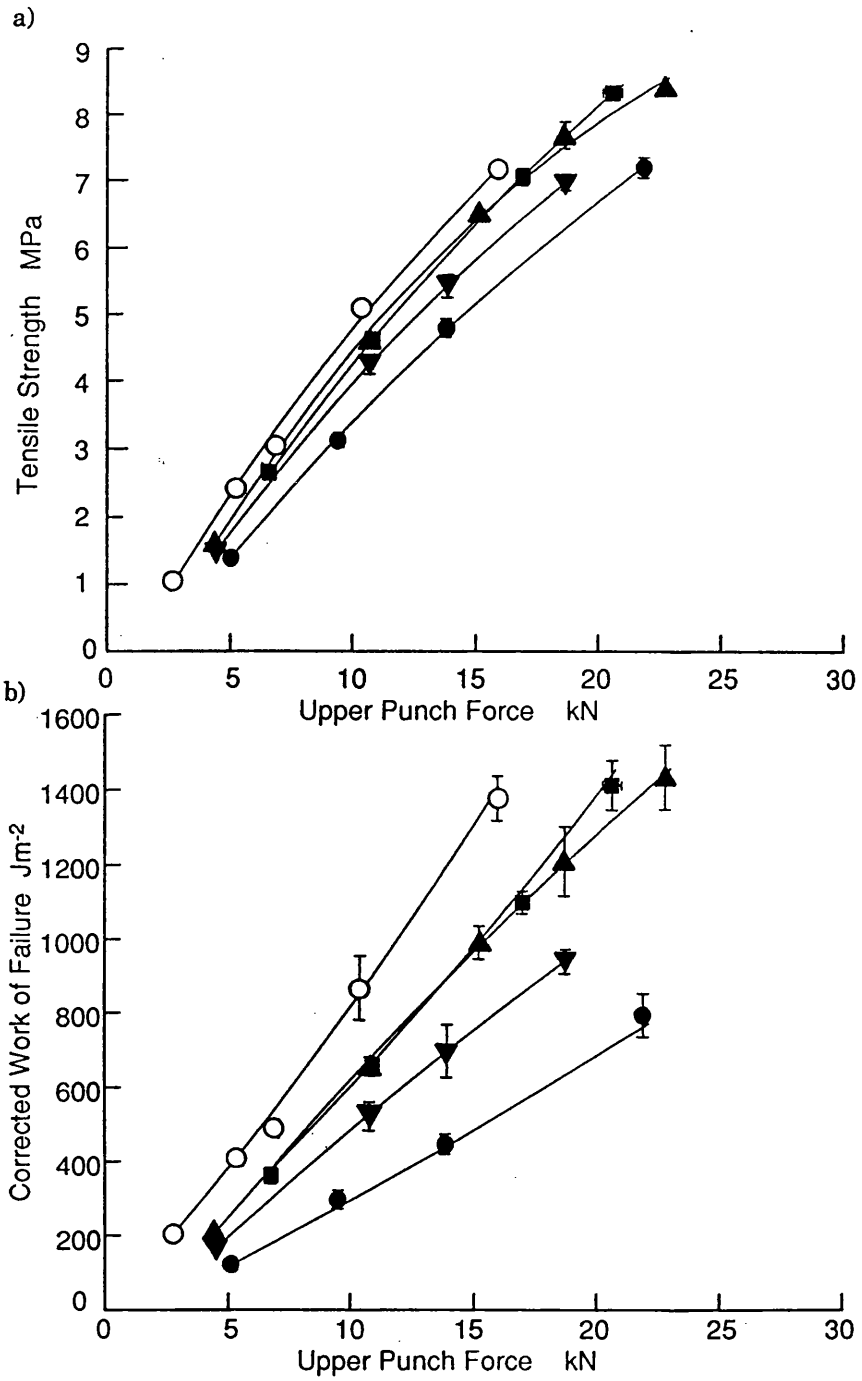


Figure 3.9 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets produced from granules prepared with and dried from varying levels of water above or equal to 66.6 $\%^{w}/_{w}$.
Note: Error bars represent 95% confidence limits.
Key: ○ Ungranulated MCC.

- ● Granules prepared with and dried from 66.6 $\%^{w}/_{w}$ water.
- ■ Granules prepared with and dried from 80.0 $\%^{w}/_{w}$ water.
- ▲ Granules prepared with 80.0 $\%^{w}/_{w}$ water and centrifuged with the supernatant readded before drying, i.e. dried from 80 $\%^{w}/_{w}$ water.
- ▼ Granules prepared with 80.0 $\%^{w}/_{w}$ water and centrifuged, the supernatant discarded, and the sediment dried from approximately 65 $\%^{w}/_{w}$ water.

strength, although the significance of the effect of granulation fluid volume on granule strength was considered by the authors to be questionable. The reasons for the behaviour observed in the present study as the granulation fluid volume was varied are discussed below.

In the present study granulation was carried out in the absence of a soluble binder. Therefore granules must have been produced as the result of some form of bonding between microcrystals. The effect of the granulation process on compactibility was shown to be affected by the water levels in both wet massing and drying stages. Furthermore, the cracked appearance of the granules prepared from between 53.8 and 75 $\%^{w}/_{w}$ water in the wet mass (figure 3.2) suggests that the improvement in compactibility observed with increasing levels of water may in part be due to the application of a milling stage promoting formation of fresh surfaces in granule preparations, which may have been potentiated as the result of uneven stresses produced in particles during drying. However, granules prepared from wet masses with water levels at or above 75.0 $\%^{w}/_{w}$ water appear to have relatively open structures (figure 3.3) and it is considered unlikely that the high porosity arose solely as the result of milling since granules prepared using 53.8 and 66.6 $\%^{w}/_{w}$ water were also milled.

In section 3.4.1 above it was suggested that in wet granules of MCC, the surface tensional and capillary forces within granules act to collapse the granule as drying proceeds and the water - air interface recedes into the granules. Further, it is suggested here that by reducing wet mass cohesion during wet granulation, the presence of excess water reduces granule densification. In addition, it is proposed that at the higher levels of water, particles are excessively overwetted and surface tension forces during drying not only exist within granules, but also between granules. Thus, as opposed to drying of wet granules, during drying of pastes or slurries, the solid phase within the slurry is held in tension at the receding air - water interface which may reduce the extent of granules collapse. Furthermore, for granules or particles compared to pastes and slurries, the forces of contraction due to evaporation of water from capillaries are not expected to be opposed to a great extent by forces external to individual particles. However, in the case of drying slurries and pastes, the forces of contraction within an area of the bed may be considered to be partially or completely counterbalanced by forces from the perimeter tending to resist the shrinkage stresses. The differences suggested

immediately above between the drying stresses within a granule bed and within a slurry are shown schematically in figure 3.10. Resistance to granule collapse and uneven drying stresses may result in reduced intragranular bonding and some disruption of the internal structure of the resulting granules with the effect of increasing the number of dislocations within the particles. The above effects singularly or in combination may lead to improved compactibility when granules are dried from slurries rather than from masses which have not been overwetted, although complete verification of this theory was beyond the scope of the present study.

3.5 Design of further studies

It was decided that further analysis of the effect of various treatments and processes on the compactibility of MCC following wet granulation in the present study should be carried out using granules containing 41.2 $\%^{w}/_{w}$ water. This concentration level was considered to be most appropriate as a basis for comparison since this level resulted in granules which did not need to be milled before compaction and gave granules with low compactibility which would act as a useful basis for evaluating the improving influence of various treatments.

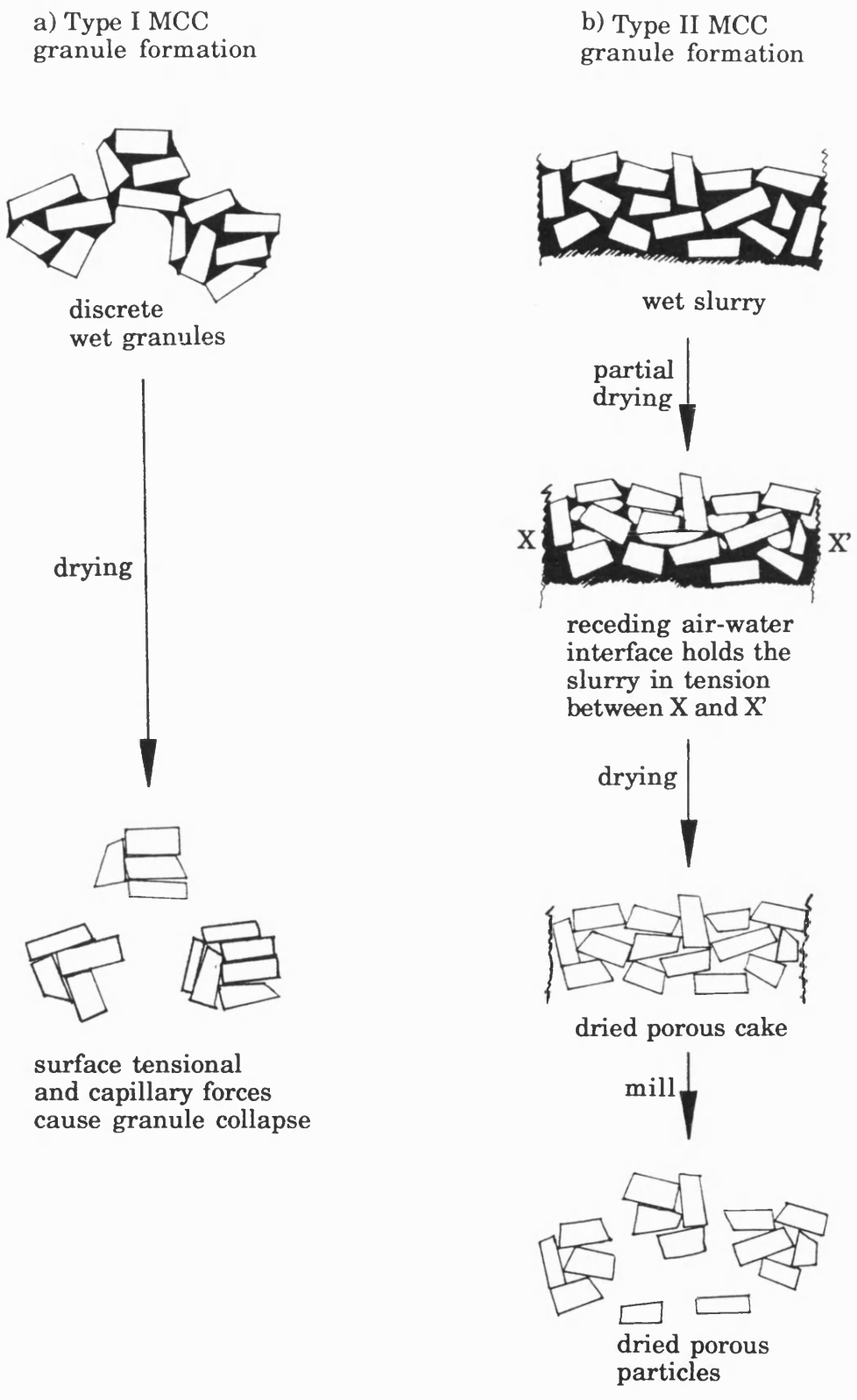


Figure 3.10 Schematic diagram showing the surface tensional forces occurring during drying of a) wet granules, and b) pastes / slurries.

Chapter 4. A study of the effect of granulation process conditions on the physico-mechanical characteristics of MCC

4.1 Objectives

The aims of this part of the study were to further characterise the effect of the interaction of water with MCC during wet granulation. The effects of impellor speed during wet massing, granulation time, and storage of the wet mass prior to drying on the mechanical characteristics of tablets produced from MCC granulated with water were investigated.

4.2 Materials and methods

Granules were prepared batchwise using 150 g MCC (Emcocel 50M, lot number 8261, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) together with 105 g distilled water which corresponded to 41.2 $\%^{w}/_{w}$ water in the wet mass. The general granule preparation method described in section 3.2.1 was used except that the granulation speed and time was varied between batches as described below. Using a granulation time of 3 minutes, the use of each of three impellor speeds were investigated:- approximately 700 rev min^{-1} (speed setting 3); approximately 1,000 rev min^{-1} (speed setting 5); and approximately 1,450 rev min^{-1} (speed setting 8). Although the actual impellor speeds as stated above are only approximate values and derive from manufacturers data, the impellor speeds were considered to be reproducibly similar for different granule batches prepared using the same speed setting. In addition, using an impellor speed of 1,450 rev min^{-1} (speed setting 8), two granulation times; 3 and 1.5 minutes, were investigated.

Immediately following preparation the wet masses produced were passed through a screen having an aperture diameter of 1.7 mm (10 mesh) and tray dried using the method described in section 3.2.2. In addition, granules were prepared using an impellor speed of approximately 1,000 rev min^{-1} (speed setting 5) and a granulation time of 3 minutes but stored for 24 hours in a triple layer of sealed polythene bags prior to screening and drying using the method described immediately above. In an attempt to eliminate possible effects caused by differences in granule size distribution between the differently prepared granules on the subsequent physico-mechanical characteristics (section 5.3), granule size

standardisation was performed as described in section 3.2.2. Tablet compaction and assessment of the mechanical characteristics of tablets were performed as described in sections 2.2.8 and 2.2.9 respectively. The satisfactory flow characteristics of the granules allowed tablets with acceptable weight uniformity to be prepared without additional vibration of the feed shoe. The bulk densities and packing characteristics of size standardised granules were determined using the appropriate techniques described in sections 2.2.6, and 2.2.7. Scanning electron micrographs were obtained for particles with sieve diameters between 90 and 180 μm using the method described in section 2.2.2.

4.3 Results and discussion

All granulated products exhibited inferior compactibility in comparison with ungranulated MCC (figure 4.1), perhaps due to increased intragranule bonding as discussed in section 3.4.1. For granules prepared using a granulation time of 3 minutes, an increase in impellor speed resulted in a progressive decrease in the strength and work of failure of tablets produced. Furthermore, for granules prepared at the highest speed (at approximately 1,450 rev min^{-1}), a reduction in granulation time resulted in an improvement in the granule compactibility. For granules prepared using an impellor speed of 1,000 rev min^{-1} with a granulation time of 3 minutes, the mechanical properties of tablets prepared from granules dried immediately was superior to that of granules dried following storage for 24 hours (figure 4.1).

The effect of granulation time and impellor speed on the compaction characteristics of MCC has not been discussed previously. However, Hancock et al (1991) reported that the consistency of MCC wet massed with water, and thus presumably liquid distribution and / or wet granule densification, varied with the time over which wet mixing was performed, the nature of the variation being dependent on the proportion of water in the wet mass. At the 33.3 $\%^{w}/_{w}$ water level, an equilibrium state was found to be achieved within 2 minutes, whereas at 52.4 and 61.5 $\%^{w}/_{w}$ water levels the equilibration period was longer (Hancock et al, 1991). In the present investigation, granules were prepared with a water content of 41.2 $\%^{w}/_{w}$. Although the granulation conditions used in the present study differed from those used by Hancock et al (1991), it is considered possible that in the present study, for granules prepared using the highest speed, the reduction in granule compactibility associated with increased granulation time

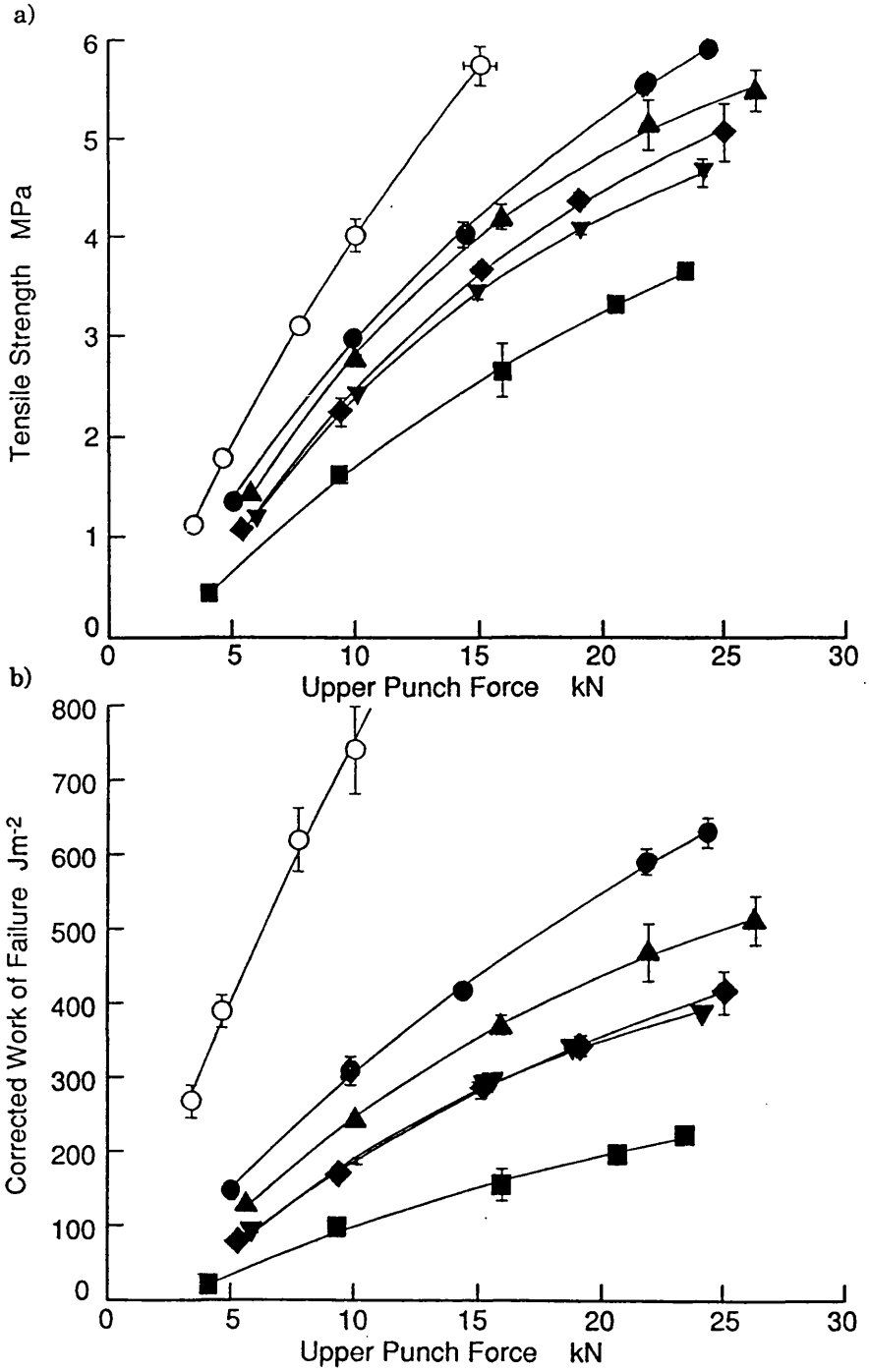


Figure 4.1 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for granules prepared using different wet massing conditions. Note: Error bars represent 95% confidence limits.
Key: ○ Ungranulated MCC.
- ● Granulation speed; approx. 700 rev min-1 (setting 3), wet massing time; 3 mins., dried immediately following preparation.
- ▲ Granulation speed; approx. 1000 rev min-1 (setting 5), wet massing time; 3 mins., dried immediately following preparation.
- ◆ Granulation speed; approx. 1450 rev min-1 (setting 8), wet massing time; 1.5 mins., dried immediately following preparation.
- ■ Granulation speed; approx. 1450 rev min-1 (setting 8), wet massing time; 3 mins., dried immediately following preparation.
- ▼ Granulation speed; approx. 1000 rev min-1 (setting 5), wet massing time; 3 mins., stored 20 hours before drying.

may wholly or partially be due to incomplete granulation fluid distribution and / or wet granule densification after the lower granulation time (1.5 minutes), which may be associated with the presence of some 'under-granulated' particles in the size standardised product. As suggested in the discussion in section 3.4.1, for MCC granules prepared with approximately 40 $\%^{w}/_{w}$ water or below, a reduction in the water content results in less intraparticle bonding within dried granules and thus improved granule compactibility.

An increase in granulation time using a constant granulation speed, and an increase in impellor speed using a constant granulation time were also found to result in increased granule poured and tapped bulk densities and a reduction in granule friabilities (table 4.1). Thus, granule compactibility (figure 4.1.) was found to be approximately inversely related to bulk density and directly related to friability, which is in general agreement with the results discussed in section 3.4.1. Increased impellor speed may be considered to have the effect of increased shear applied during granulation. In section 3.3.1 it was shown that granule bulk density and granule friability were approximately, although not exactly, related to granule porosity. Hunter & Ganderton (1973) reported that increasing the shear during granulation resulted in a reduction in granule porosity for granules prepared from either lactose or calcium phosphate granulated with water only, which is similar to the trends reported in the present study. An increase in granulation time has also been reported by other workers to reduce granule friability for a mixture of MCC and lactose granulated with water (Remon & Schwartz, 1987) and for calcium phosphate (Ganderton & Hunter, 1971).

Table 4.1. The effect of granulation process variables on the poured and tapped bulk densities of MCC

Granulation speed (setting no.)	Granulation time (mins)	Wet mass storage time (hrs)	Bulk density (gcm^{-3}) Poured	Tapped	Carr's index	Hausner ratio	Granule friability (%)
3	3	0	0.30	0.38	21.1	1.27	62
5.5	3	0	0.33	0.41	19.5	1.24	54
8	3	0	0.40	0.50	20.0	1.25	40
8	1.5	0	0.36	0.44	18.2	1.22	65
5.5	3	24	0.41	0.50	18.0	1.22	36

In the present study, scanning electron micrographs of granules qualitatively indicated that the increased bulk density with higher impellor speeds may be attributable to an increase in individual particle density rather than simply improved particle packing (figure 4.2). Although granule bulk and tapped density were affected by the granulation conditions, the Hausner ratio and Carr's compressibility index were, perhaps surprisingly, only slightly affected by differences in the granulation conditions (table 4.1). This may be considered to provide further evidence of differences in the relative effect of granulation on bulk and surface behaviour of granules discussed in section 3.3. In addition, the similarity of the Hausner ratio and Carr's compressibility indices for the different granule types suggests that despite differences between their bulk densities, granules prepared under the various conditions exhibit similar flow characteristics.

Allowing the water to 'soak' into the excipient for 24 hours before drying resulted in increased densification of the resulting dried granules (table 4.1) in addition to reduced compactibility (figure 4.1). The present results thus suggest that the greater the 'interaction' of MCC with water, achieved either by increasing the granulation time or impellor speed, or by storage of the wet granules before drying, the greater the densification of the resulting granules and the greater the reduction in granule compactibility. These results are also consistent with the the quasi-hornification theory proposed in section 3.4.1 to explain the effect of wet granulation on the physico-mechanical characteristics of MCC.

The results of the present study suggest that for formulations containing MCC, any reduction in granulation intensity, that is granulation speed and/or wet massing time would result in a product having improved compactibility. However, insufficient kneading time may result in uneven distribution of the granulation fluid throughout the dry powder, and sub-optimal granule growth (Carstensen et al, 1976; Cliff, 1990). Physical aspects of the granulation process in water granulated formulations consisting of sucrose, starch and lactose have been discussed by Carstensen et al (1976) and Zoglio et al (1976). When the powders are first wetted, a fraction becomes overwet forming large aggregates, and a fraction remains un-wetted. Distribution of water was subsequently improved as a result of further agitation of the wet product forming both small and large particles. Finally, at a certain granulation time an equilibrium granule size and size distribution was reached providing an appropriate proportion of fluid was present.

Figure 4.2 Scanning electron photomicrographs of ungranulated MCC and MCC granules prepared using different wet massing conditions. (Note: column I shows a general view of groups of particles at a lower magnification, and column II shows details of individual agglomerates).

I II

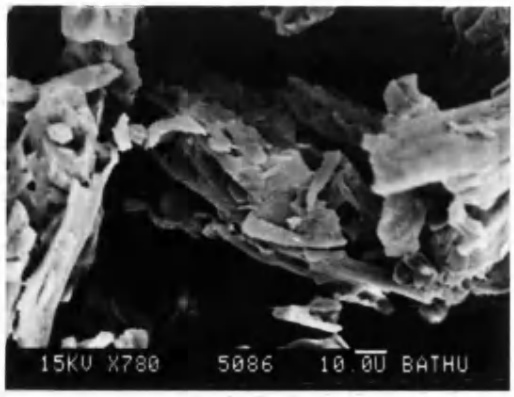
Ungranulated MCC.

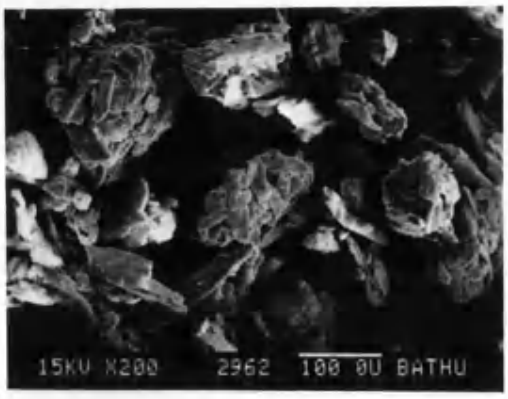
Granulation speed; approx. 700 rev min-1 (setting 3), wet massing time; 3 mins., dried immediately following preparation.

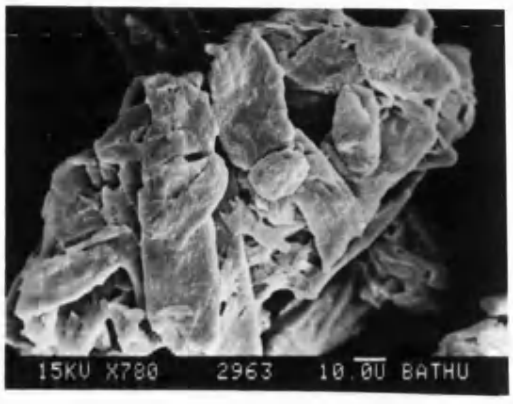
Granulation speed; approx. 1000 rev min-1 (setting 5), wet massing time; 3 mins., dried immediately following preparation.

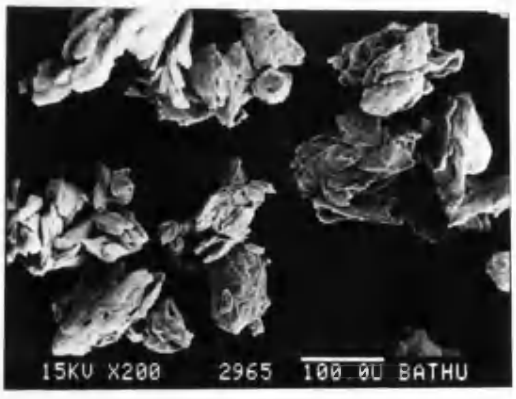
Granulation speed; approx. 1450 rev min-1 (setting 8), wet massing time; 3 mins., dried immediately following preparation.


15KV X200 5085 100.0U BATHU


15KV X780 5086 10.0U BATHU

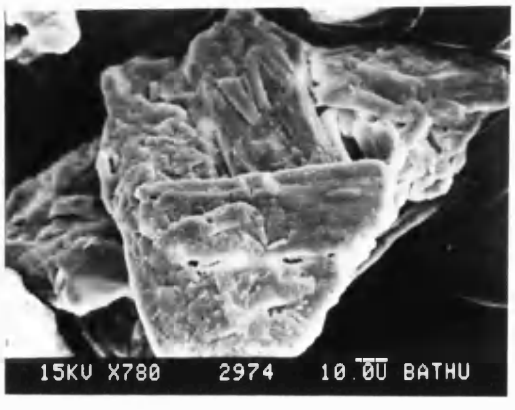

15KV X200 2962 100.0U BATHU


15KV X780 2963 10.0U BATHU


15KV X200 2965 100.0U BATHU


15KV X780 2966 10.0U BATHU


15KV X200 2975 100.0U BATHU


15KV X780 2974 10.0U BATHU

Excessive blending caused alteration of the packing arrangement within the wet granules, and resulted in an increased wet granule density and reduced porosity which was considered at least partly due to increased dissolution of soluble components in the formulation contributing to a reduction in granule porosity (Zoglio et al, 1976). It was therefore suggested that an optimal kneading time was needed which was dependent on the period required to reach equilibrium granule size without causing excessive granule densification and dissolution of soluble formulation components. However, consideration of the results presented here, suggests that industrial formulations containing MCC in addition to dissolved binder(s) may benefit from addition of some or all of the MCC towards the end of the wet massing stage so that the high compactibility of the excipient is retained. It is considered unlikely that this would significantly reduce the value of MCC as an agent for reducing the sensitivity of the formulation to inadvertent over-wetting, a benefit suggested by Sheth et al (1980).

In addition, the present results highlight the need for strict controls on the granulation conditions and on the wet granule storage time prior to drying in order to prepare dried products with consistent compaction characteristics and bulk densities.

Chapter 5. A study of the influence of particle size on the physico-mechanical characteristics of ungranulated and granulated MCC

5.1 Objectives

The aims of this part of the study were to characterise the influence of particle size and particle size distribution on the physico-mechanical characteristics of ungranulated and wet granulated MCC. A major objective of the following study was to investigate whether an increase in particle size was wholly or partially responsible for the loss in compactibility of MCC following wet granulation.

5.2 Materials and methods

Granules were prepared batchwise using 150 g MCC (Emcocel 50M, lot number 8261, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) together with 105 g distilled water which corresponded to 41.2 % $^{w}/_{w}$ water in the wet mass, using the general method described in section 3.2.1. Wet granules were screened using an aperture diameter of 1.7 mm (10 mesh) before tray drying by the method described in section 3.2.2. Granules were separated into different sieve diameter fractions using the method described in section 2.2.1 except that the nominal aperture diameters of sieves used were 500 µm, 355 µm, 250 µm, 180 µm, 90 µm, 75 µm, 63 µm, and 45 µm. It is recognised that use of such a large number of sieves in a single stack may result in poor sieving efficiency. However, the use of eight sieves in the stack was considered reasonable since the granulated material contained relatively few particles with a sieve size greater than 250 µm (table 5.2), and the granule bed rapidly passed through the first three sieves. In addition, ungranulated MCC powder sieved using the technique described above was used in the present investigations.

Sieve fractionation of granulated and ungranulated MCC yielded insufficient quantities of some particle diameters to allow complete comparative characterisation to be carried out. For this reason, proportional reconstitution of sieve fractions of ungranulated and granulated MCC was carried out as shown in table 5.1a. Since ungranulated powder did not contain particles with a sieve diameter greater than 180 µm, proportional recombination of coarser sieve

fractions was only carried out using granulated material (table 5.1b). In addition, a sample containing granules combined according to the formula presented in table 3.1. was prepared. In all cases, combined fractions were mixed by shaking for three minutes in a polythene bag prior to physico-mechanical characterisation.

Scanning electron micrographs were obtained for particles with various sieve diameters using the method described in section 2.2.2. In addition, the poured bulk density of individual and recombined size fractions of ungranulated and granulated MCC were determined using the technique described in section 2.2.6. Tablet compaction and assessment of the mechanical characteristics of tablets were performed as described in sections 2.2.8 and 2.2.9 respectively. Although all ungranulated products required additional vibration of the feed shoe in order to obtain uniform die filling, such a procedure was not necessary in the cases of granulated MCC products which had acceptable flow characteristics.

Table 5.1. Sieve fractions and proportional reconstitutions of different sieve fractions of granulated and ungranulated MCC

a. Granulated and ungranulated MCC

Sieve fraction	Proportion of sieve fraction in sample	Sample identification
less than 45 µm	15%	less than 75 µm
45 - 63 µm	40%	
63 - 75 µm	45%	
75 - 90 µm	100%	75 - 90 µm
90 - 180 µm	100%	90 - 180 µm

b. Granulated MCC only

Sieve fraction	Proportion of sieve fraction in sample	Sample identification
180 - 250 µm	100%	180 - 250 µm
250 - 355 µm	85%	greater than 250 µm
355 - 500 µm	15%	

5.3 Results and discussion

5.3.1 Physical characteristics of different particle size fractions of ungranulated and granulated MCC

In the absence of dissolved binders, wet granulation of MCC powders was found to produce only limited particle aggregation (table 5.2).

Table 5.2. Particle size distribution of ungranulated and granulated MCC

Sieve fraction	Percentage of particles by weight	
	Ungranulated MCC	Granulated MCC
less than 45 μm	32.8	0.6
45 - 63 μm	19.5	3.5
63 - 75 μm	8.7	3.3
75 - 90 μm	29.4	13.5
90 - 180 μm	9.6	55.0
180 - 250 μm	0	18.9
250 - 355 μm	0	3.6
355 - 500 μm	0	0.9
greater than 500 μm	0	0.9

The bulk densities of both ungranulated and granulated MCC decreased with an increase in particle size (table 5.3). This apparently contradicts the findings of Bolhuis & Lerk (1973), Doelker et al (1987a) and Whiteman & Yarwood (1988) who reported that 'large' particle size grades (corresponding to Avicel PH-102) of commercial ungranulated MCC materials exhibited higher poured and tapped bulk densities than 'medium' size grades (corresponding to Avicel PH-101). It was considered that the apparent discrepancy between the results of the present study and that of these workers was due to their use of wide

Table 5.3. Poured bulk densities of individual and recombined size fractions of granulated and ungranulated MCC

Sieve size fraction	Poured bulk densities (gcm^{-3})	
	Ungranulated MCC	Granulated MCC
less than 45 µm	0.30	insufficient material
45 - 63 µm	0.28	0.53
63 - 75 µm	0.26	0.52
75 - 90 µm	0.25	0.49
90 - 180 µm	0.21	0.43
180 - 250 µm	no material	0.40
250 - 355 µm	no material	insufficient material
355 - 500 µm	no material	insufficient material
greater than 500 µm	no material	insufficient material
Size standardised, less than 75µm (using formula in table 5.1a)	0.27	0.52
Size standardised greater than 250 µm (using formula in table 5.1b)	no material	0.40
Blend of granules (using formula in table 3.1)	no material	0.40

size distributions present in the commercial size grades of MCC tested in those studies. The effect of particle size on bulk density reported in the present study is consistent with results reported for spray dried substances containing dissolved solids reported by Duffie & Marshall (1953), and may in part be associated with a decrease in intraparticle density with increased particle size for both ungranulated and granulated MCC. Some evidence of the latter phenomenon can be seen in the electron micrographs for different size fractions of ungranulated and granulated MCC (figure 5.1), although comparison of intraparticle porosity from the micrographs is somewhat subjective.

Perhaps more significantly, considering data for any particle size fraction, granulated products exhibited higher poured bulk densities in comparison with ungranulated MCC (table 5.3). This was considered to be consistent with granulation increasing the intraparticle density and shape regularity of particles of all sizes as assessed from electron micrographs (figure 5.1). Further, the observed increase in bulk density arising from granulation was considered consistent with the theory of granulation causing increased intraparticle bonding which is discussed in section 3.4.1. Comparison between data presented in table 5.3 also reveals that the bulk density of ungranulated MCC particles with a sieve diameter in the range 90 - 180 μm was 70% of that exhibited by ungranulated MCC particles with a sieve diameter 45 - 63 μm. Further, comparing these sieve fractions of granulated MCC; particles with a sieve diameter 90 - 180 μm exhibited a poured bulk density which was approximately 80% of that exhibited by particles in the size range 45 - 63 μm. In contrast, for a given size fraction, ungranulated MCC exhibited a bulk density which was approximately half that of granulated MCC. These differences strongly suggest that the influence of particle size on the physical behaviour of MCC powder was much less than the effects due to granulation. Qualitatively, during tablet production, granulation was also found to have a more significant effect on powder flow than particle size of ungranulated MCC.

5.3.2 Compaction characteristics

The compaction profiles for the individual and proportionally reconstituted sieve fractions of granulated and ungranulated MCC, together with that for ungranulated MCC with a particle size distribution as received are shown in figure 5.2. Tablets prepared from ungranulated MCC exhibited substantially greater

Figure 5.1 Scanning electron photomicrographs of sieve fractions ungranulated MCC and MCC granules. (Note: column I shows a general view of groups of particles at a lower magnification, and column II shows details of individual agglomerates).

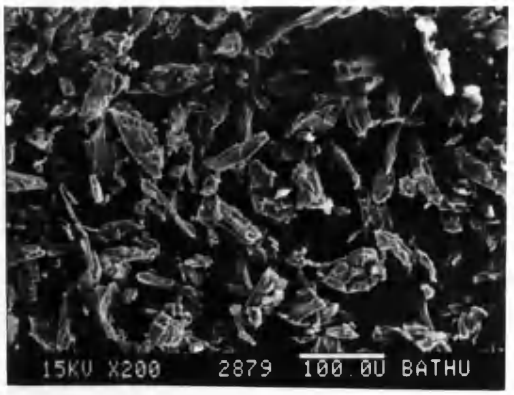
I II

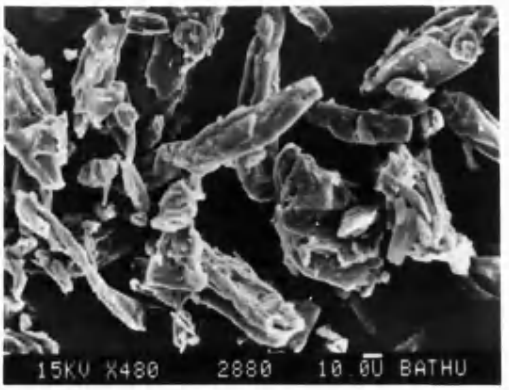
Ungranulated MCC; less than 45μm

MCC Granules; less than 45μm

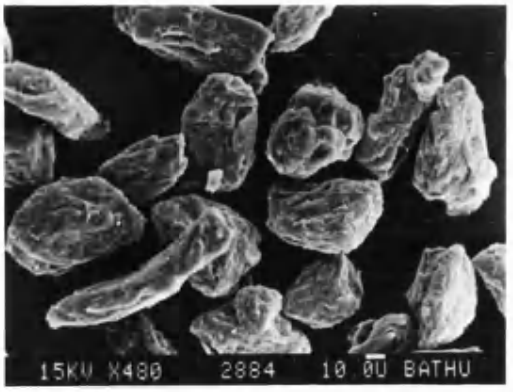
Ungranulated MCC; 45 - 63μm

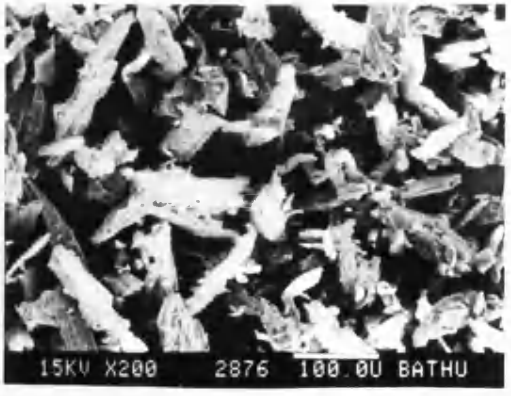
MCC Granules; 45 - 63μm

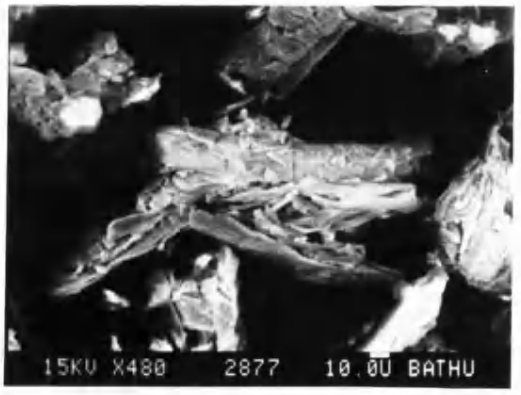

15KV X200 2879 100.0U BATHU

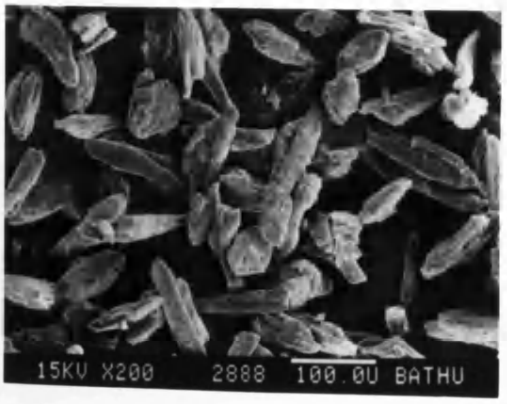

15KV X480 2880 10.0U BATHU


15KV X200 2883 100.0U BATHU


15KV X480 2884 10.0U BATHU


15KV X200 2876 100.0U BATHU


15KV X480 2877 10.0U BATHU


15KV X200 2888 100.0U BATHU


15KV X480 2890 10.0U BATHU

Figure 5.1 (continued)

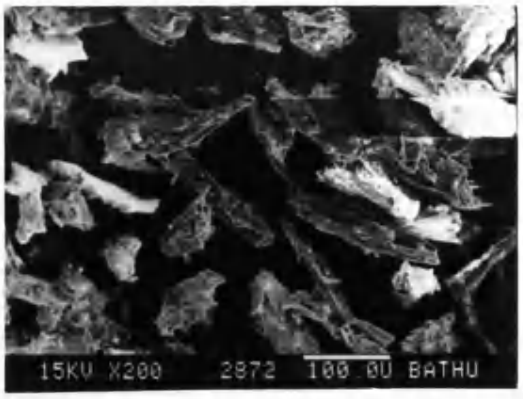
I II

Ungranulated MCC; 63 - 75μm

MCC Granules; 63 - 75μm

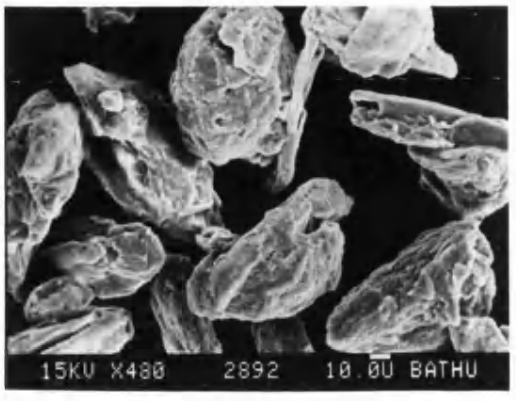
Ungranulated MCC; 75 - 90μm

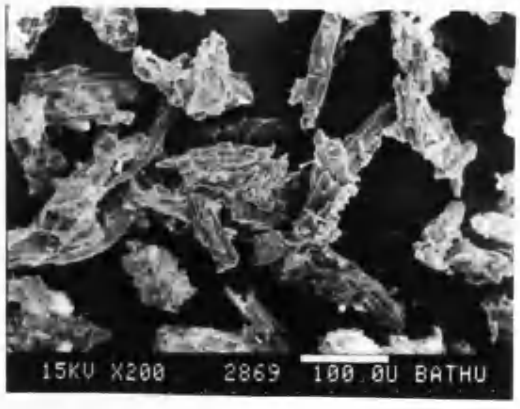
MCC Granules; 75 - 90μm

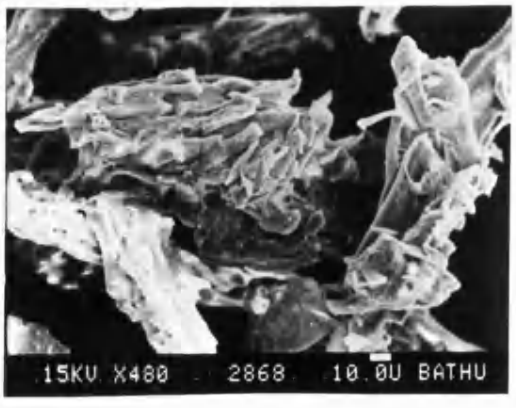

15KV X200 2872 100.0U BATHU


15KV X480 2871 10.0U BATHU


15KV X200 2891 100.0U BATHU


15KV X480 2892 10.0U BATHU


15KV X200 2869 100.0U BATHU


15KV X480 2868 10.0U BATHU


15KV X200 2930 100.0U BATHU

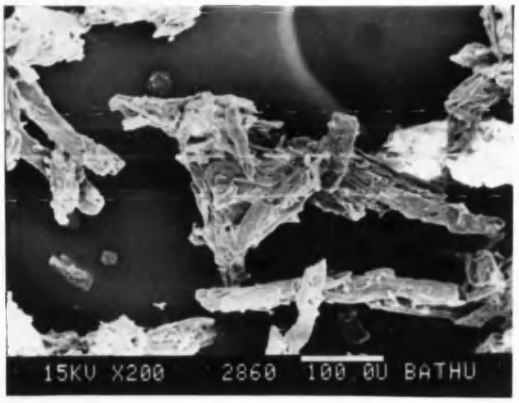

15KV X480 2931 10.0U BATHU

Figure 5.1 (continued)

I II

Ungranulated MCC; 90 - 180μm

MCC Granules; 90 - 180μm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15KV X480 2861 10.0U BATHU


15KV X200 2841 100.0U BATHU

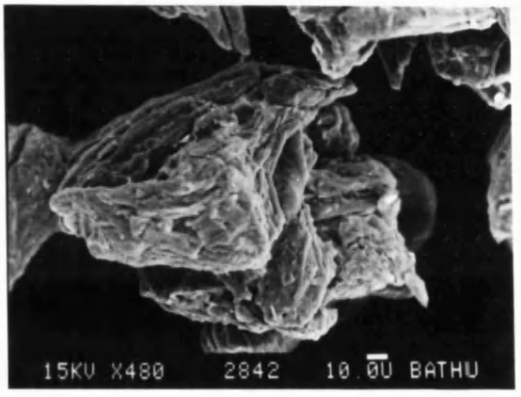

15KV X480 2842 10.0U BATHU

Figure 5.1 (continued)

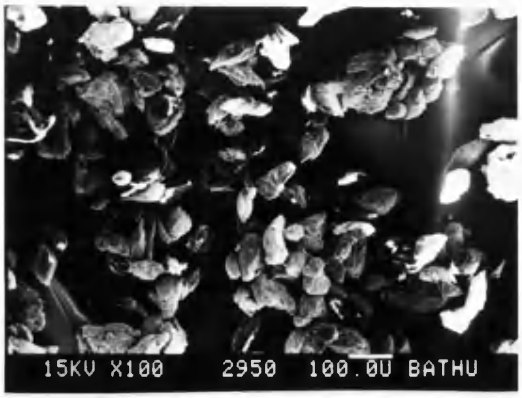
I II

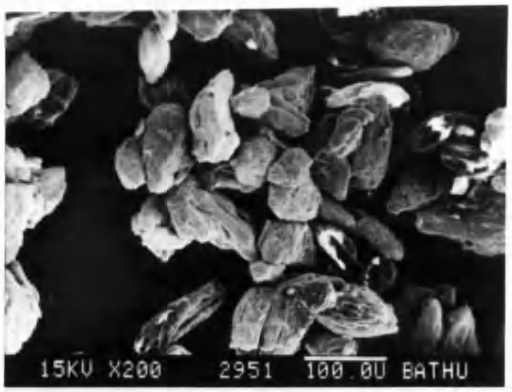
MCC Granules; 180 - 250μm

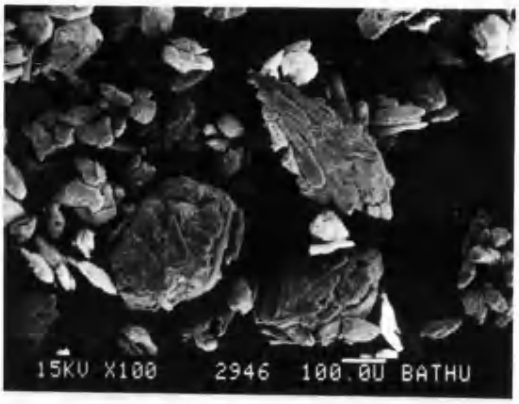
MCC Granules; 250 - 355μm

MCC Granules; 355 - 500μm

MCC Granules; greater than 500μm

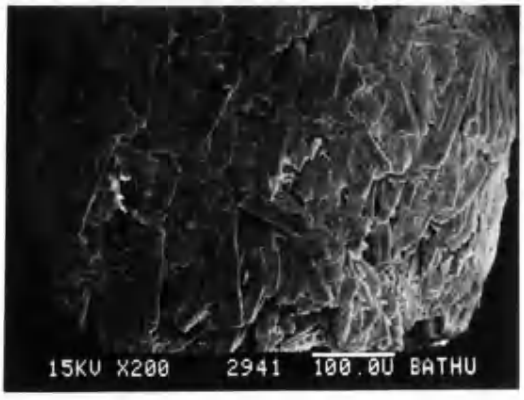

15KV X100 2950 100.0U BATHU

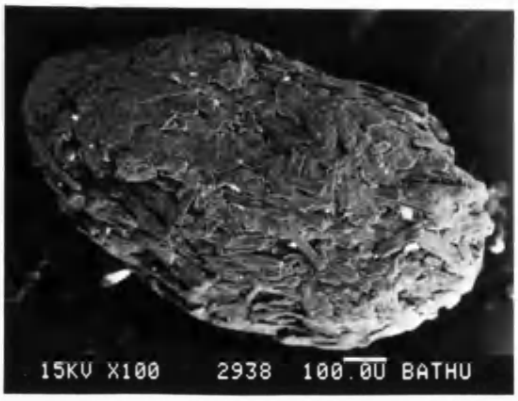

15KV X200 2951 100.0U BATHU

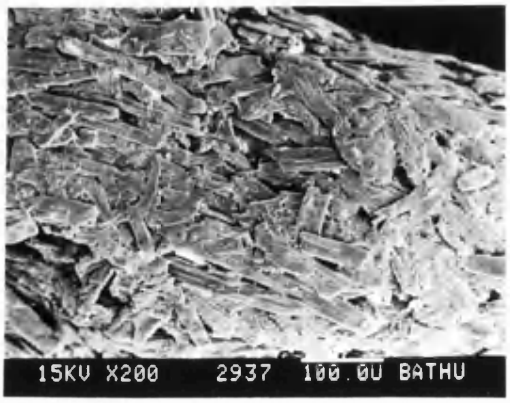

15KV X100 2946 100.0U BATHU


15KV X200 2947 100.0U BATHU


15KV X100 2940 100.0U BATHU


15KV X200 2941 100.0U BATHU


15KV X100 2938 100.0U BATHU


15KV X200 2937 100.0U BATHU

tensile strength and work of failure than compacts prepared from granules, irrespective of particle size.

With the exception of the size standardised granules recombined using the formula in table 3.1 and which were prepared to eliminate the effect of particle size on mechanical characteristics for studies carried out in Chapters 3, 4, 7 and 12, particle size or size distribution had little effect on tablet tensile strength for either ungranulated or granulated MCC (figure 5.2a). However, granules recombined using the formula in table 3.1 produced tablets with a higher tensile strength in comparison with the other granulated particle size fractions and combined fractions (figure 5.2a). This may be associated with the comparatively wide particle size distribution within the granule sample recombined using the formula in table 3.1 facilitating closer interparticle packing within the tableting die and resulting in a higher number of bonding contact points within the compressed tablet, in comparison with tablets prepared at comparable forces from granules with a narrower size distribution.

The compaction force - work of failure profiles for samples of ungranulated MCC suggest that the toughness of tablets produced from sieve fractions less than 75 μm in diameter recombined using the formula in table 5.1a, and from the 75 - 90 μm sieve fraction were similar (figure 5.2b). However, the latter two sieve factions yielded slightly tougher tablets than 90 - 180 μm sieve fraction and unsieved material (figure 5.2b). It should, however, be noted that these differences were only slight and it is considered reasonable to conclude that the influence of particle size on the compactibility of ungranulated MCC was marginal. This conclusion is consistent with findings of other workers who showed that an increase in particle size had little effect on the strength of tablets produced from either Avicel PH-101 (McKenna & McCafferty, 1982) or Avicel PH-102 (van der Watt, 1987), and no effect on yield pressure (Roberts & Rowe, 1986 and 1987). In addition, Bolhuis & Lerk (1987) found little difference between the strength of tablets produced from either Avicel PH-101 or PH-102 both in the presence and absence of magnesium stearate. Although Doelker at al (1987) and Whiteman & Yarwood (1988) reported that for materials of the same commercial form including the Avicels the 'large' size grades produced slightly weaker tablets in comparison with the 'medium' size grades in the presence of magnesium stearate, these effects were only small.

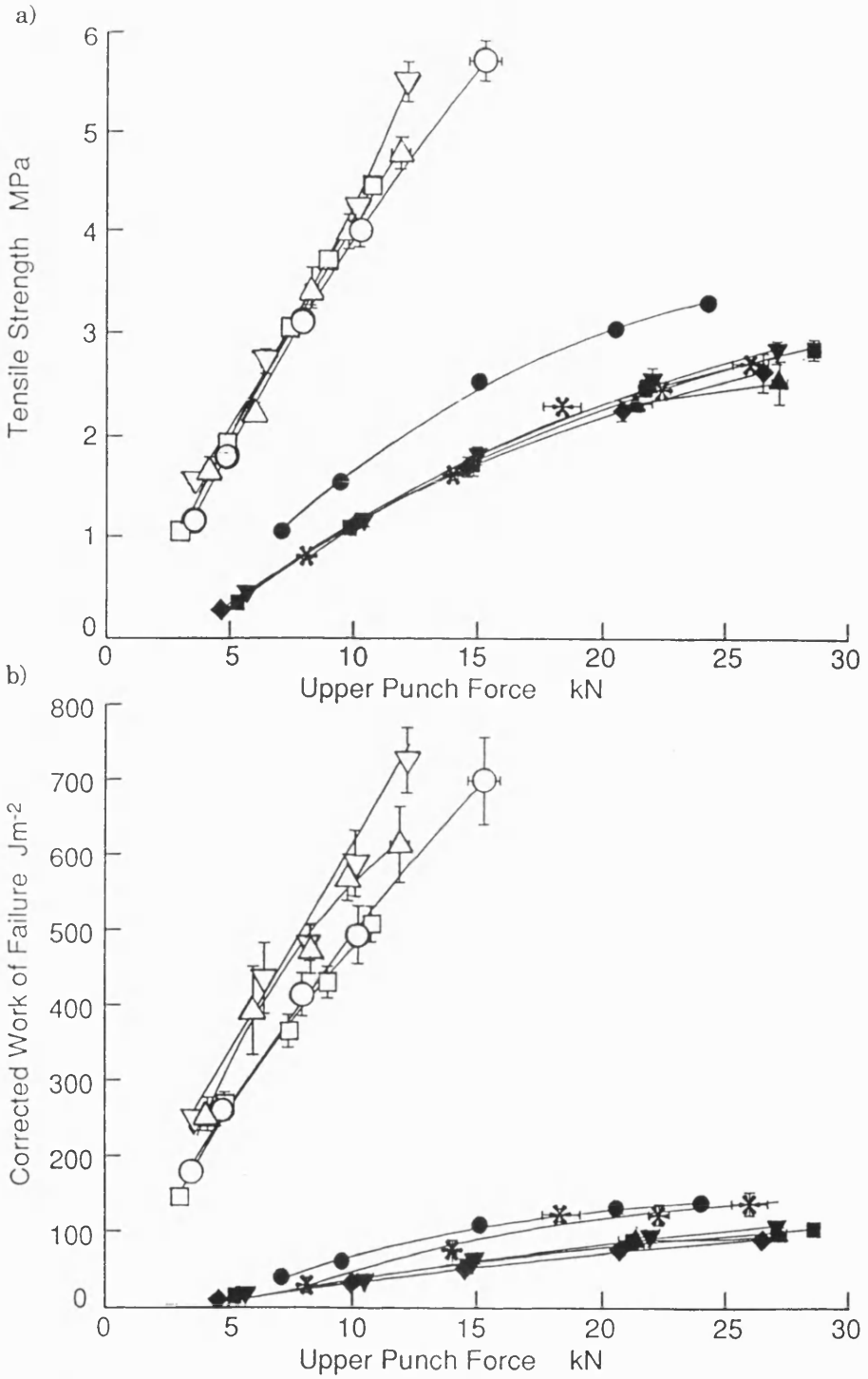


Figure 5.2 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for individual and proportionally recombined sieve fractions of ungranulated and granulated MCC, and for ungranulated MCC with a particle size distribution as received. Note: Error bars represent 95% confidence limits.

Key: Ungranulated MCC:i)As received; ○ ii) less than 75 μm; △ iii) 75 - 90 μm; ▽ iv) 90 - 180 μm; □ .

Granulated MCC: i)Proportionally recombined using the formula in table 3.1; ● ii) less than 75 μm; ▲ iii) 75 - 90 μm; ▼ iv) 90 - 180 μm; ■ v) 180 - 250 μm; ◆ vi) greater than 250 μm; ✻ .

The toughness of tablets produced from (a) recombined MCC granules greater than 250 μm and (b) size standardised MCC prepared according to the formula presented in table 3.1 was slightly greater than the other size fractions of granules (figure 5.2b). It was considered that the improved toughness of tablets prepared from granular materials (a) and (b) may have been due to packing effects discussed above. Although the compactibility of a given MCC sample will be related to packing in addition to any other effects, the data shows that particle size has relatively little effect on the compactibility of MCC in comparison with the loss in compactibility observed as a result of wet granulation. This further supports the theory developed in section 3.4.1 where it was proposed that the loss in compactibility upon granulation was due to alterations in the material itself. However, in order to minimise the small effects caused by different size distributions within granules prepared by different techniques in other studies in the present investigation, it was considered desirable to use a standardised particle size distribution of MCC granules. Importantly, the present results also suggest that it may be possible to increase the particle size and poured bulk density of MCC, thereby improving the flowability of MCC, without necessarily causing a significant reduction in the compactibility of MCC.

Chapter 6. A study of the relative influence of drying techniques on the physico - mechanical properties of MCC granules

6.1 Objectives

In section 3.4.1 it was suggested that the effect of wet granulation and drying on the physico-mechanical characteristics of MCC are due to increased intragranule bonding by a mechanism similar to that occurring in hornification of cellulose fibres. In the context of paper-making it has been reported that hornification of cellulose fibres may be influenced by the drying technique employed (section 1.4.3). For this reason investigation of the effect of drying technique on the subsequent physico-mechanical characteristics of wet granulated MCC may provide further information regarding the reduction in compactibility of the excipient from increased intragranule bonding. Another objective of this part of the present study was to examine drying methods by which granule compactibility may be improved.

6.2 Materials and Methods

6.2.1 Preparation of standardised wet mass

Wet granules were prepared using Emcocel 50M (Emcocel 50M, lot number 8259, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) and distilled water only. Granulation was performed using a high-speed mixer / granulator fitted with a microwave-vacuum drying facility (Spectrum Processor, T.K. Fielder Ltd., U.K.), the principle features of which are shown in figure 6.1. During granulation, the microwave output and vacuum pump were switched off. Since it was not possible to prepare one wet granule batch of sufficient size to yield material for drying by all of the selected techniques, wet granules were prepared in three batches. The amount of MCC and water used in the preparation of each batch are shown in table 6.1. Although batch 3 was smaller than batches 1 and 2 (table 6.1), each batch was granulated using similar proportions of water and under similar conditions. At time zero, granulation was initiated by commencing spraying of the required amount of distilled water onto the MCC at a pressure of approximately 2×10^5 Nm^{-2}, and agitating the powder / granule bed. The main impellor and chopper speeds used during the course of wet mass preparation are given in table 6.2.

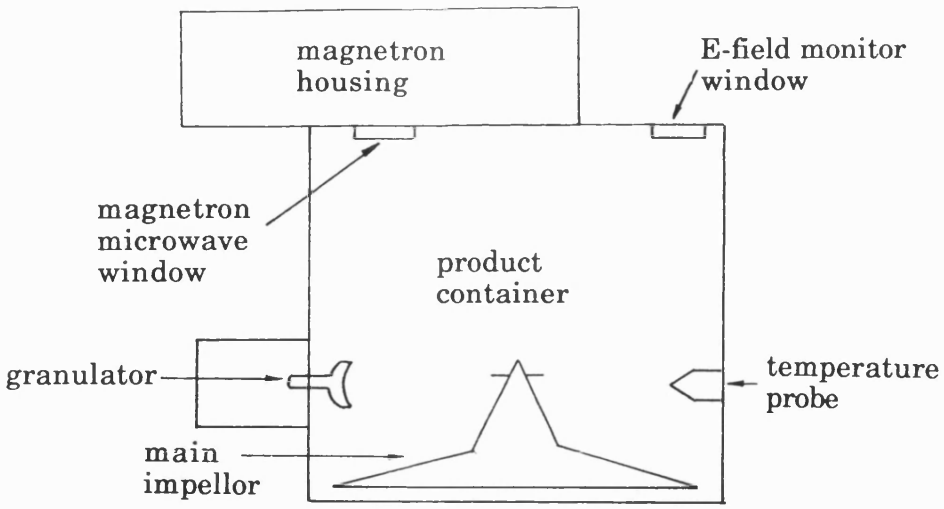


Figure 6.1 Schematic diagram of the high-speed mixer/granulator/microwave - vacuum drier (Spectrum Processor, T.K. Fielder) used for granule preparation and microwave-vacuum drying.

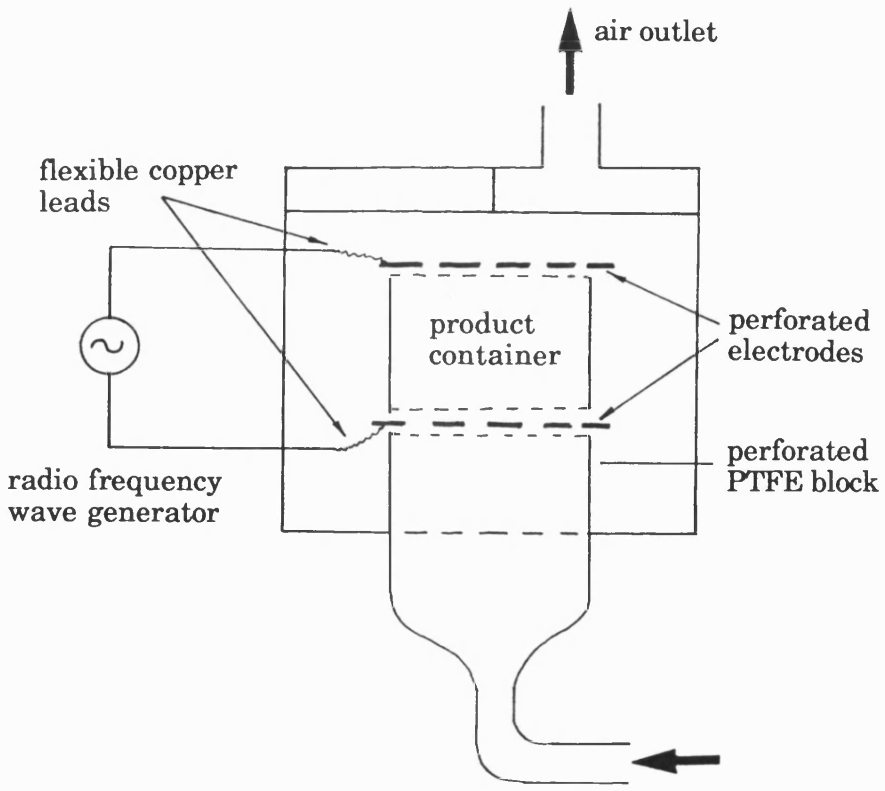


Figure 6.2 Schematic diagram of the prototype radio frequency drier used in the present study.

Table 6.1 The amount of MCC and water used in the preparation of individual granule batches

Batch No.	Mass of MCC (kg)	Mass of water (kg)	Proportion of water expressed as a percentage of the final wet mass (% $^{w}/_{w}$)
1	11.0	6.56	37.4
2	11.0	6.87	38.4
3	6.9	4.14	37.5

Table 6.2 Agitation conditions used for preparation of all batches of wet granules in the high - speed mixer / granulator

	Time period (minutes after start of fluid addition)	Main impellor speed (rev min^{-1})	Chopper speed (rev min^{-1})
Period during which granulation fluid was added	0 - 1	100	1,500
	1 - 4	200	1,500
Agitation following fluid addition	4 - 4.5	200	3,000
	4.5 - 6	250	3,000

Wet granules were discharged and sub-divided for drying using different techniques. In the case of wet granules from batches 1 and 2, drying was initiated within 30 minutes of granule preparation with the exception of microwave-vacuum dried granules dried using the "low" process type which was initiated approximately 70 minutes after wet granule preparation. Radio frequency drying was carried out at another site and wet granules from batch 3 were therefore stored for approximately 20 hours in a double layer of polythene prior to drying. Storage of wet mass prior to drying has been shown to affect the subsequent physico - mechanical properties of MCC granules (section 4.3). For this reason a

"control" sample of wet granules from batch 3 were tray dried approximately 26 hours following preparation of the wet mass. This enabled the influence of radio frequency drying to be compared with that of the other drying techniques.

6.2.2 Drying Methods

General principles of the drying techniques used in this part of the study are included in section 1.2.2. The drying conditions investigated in the present study are described below. It should be noted that for each different drying technique described below the batch number(s) from which wet mass was derived, corresponding to those in table 6.1, are given. In addition, where possible, the loss in moisture due to drying was determined using the following relationship;

$$L.O.D. = \frac{M_w - M_d}{Mw} \times 100 \qquad \text{Equation 6.1}$$

Where:-

L.O.D. = Loss of moisture on drying on a wet weight basis (% $^{w}/_{w}$)

M_w = Weight of granules immediately before drying

M_d = Weight of granules immediately following completion of the drying procedure

6.2.2.1 Tray drying to "just dry" conditions (batches 1 and 3)

Granules were dried in static beds, approximately 5 to 10 mm thick, in a convection oven at 60°C until the L.O.D. was 36 $\%^{w}/_{w}$. This was approximately equivalent to the concentration of water added to the MCC during granulation (table 6.1).

6.2.2.2 Tray drying to "over dry" conditions (batch 1)

Drying was carried out as described immediately above for "just dry" tray dried granules but for a longer period of time. For these samples the L.O.D. was 39 $\%^{w}/_{w}$ and represented removal of water beyond that added during granulation.

6.2.2.3 Drying under ambient conditions (batch 1)

Granules were dried in static beds, approximately 5 to 10 mm thick, by

exposure to the atmosphere of the laboratory (approximately 10°C at 30% relative humidity) for 18 hours. The L.O.D. was 36 $\%^{w}/_{w}$.

6.2.2.4 Vacuum oven drying (batch 1)

Wet granules were dried in a vacuum oven at 40°C and 13 Nm^{-2} using continuous pumping (Model E2M2, Edwards High Vacuum, Sussex, U.K.). The L.O.D. was 39 $\%^{w}/_{w}$.

6.2.2.5 Fluidised bed drying (batch 1)

Wet granules were dried using a laboratory - scale fluidised bed dryer (Type STREA 1, Niro Aeromatic, Abingdon, U.K.). The temperature of the inlet air was maintained at 80°C. In addition, the outlet temperature was recorded and was found to vary between 28 and 30°C. The maximum fluidisation velocity obtainable using the drier was selected for the first 2-3 minutes of drying after which the minimum fluidising velocity was employed. The L.O.D. for granules dried using this technique could not readily be determined due to loss of fine particles during drying.

6.2.2.6 Freeze-drying (batch 1)

Wet granules were frozen at -40°C for approximately 16 hours after which the moisture was removed by sublimation using a laboratory freeze drier (Super Modulyo 12K, Edwards High Vacuum, Sussex, U.K.) operated at a pressure of 15 Nm^{-2}. After two hours of drying at -20 °C the shelf temperature was increased to -10°C, and after a further four hours increased to +20°C. Drying was terminated after 18 hours after which the loss of moisture on a dry weight basis was found to be 39 $\%^{w}/_{w}$.

6.2.2.7 Microwave - vacuum drying, "high" and "low" process types (batches 1 and 2)

Microwave-vacuum drying was performed in the Spectrum Processor using electromagnetic radiation at a frequency of 2,450 MHz. For each drying cycle the jacket temperature was set to 35°C and the contents of the bowl continuously evacuated to provide an operating pressure between 43 and 50 x 10^{2} Nm^{-2}. Wet granules were dried in lots, each of approximately 6.5 kg in weight, by either a "high" or "low" drying process type. The drying conditions involved in the two process types are described further below.

Microwave drying using the Spectrum Processor can be divided into a maximum of three drying stages and transfer from one stage to the next performed automatically. When the preset conditions for the first stage were attained, the drier tripped to the second stage conditions in which the power output from the magnetrons was reduced. This reduction in microwave output was achieved by automatic repeated switching of the magnetrons from full to zero power. Similarly, once the preset selected conditions for the second drying stage were reached, the third stage was automatically entered in which the pulsed magnetron output was further reduced. The "high" and "low" process types differed only in the time over which the magnetrons were switched on during the three drying stages and thus in the microwave power supplied to the material undergoing drying during each stage. The magnetron "percentage on" time for the two process types is listed in table 6.3.

Table 6.3 Magnetron "percentage on" time during the three drying stages for microwave-vacuum drying by the "high" and "low" process types

	Stage 1	Stage 2	Stage 3
"High" process type	100 %	66 %	50 %
"Low" process type	50 %	25 %	20 %

Using the control panel on the processor, the conditions specified in table 6.4 were selected for each drying cycle. The % E-field is the proportion of "free" microwaves or the intensity of the electric field reflected from the product expressed as a percentage of the supplied or incident electric field strength. The maximum E-field and maximum product temperature were the conditions which, when either were reached, resulted in the processor automatically switching to the next drying stage. Selection of the maximum allowed E-field at a value of 90 % and the maximum allowed product temperature of between 40 and 44°C enabled the drying process to be controlled by the temperature of the product as opposed to the strength of the reflected E-field from the material since the product always reached the preset maximum temperature before 90 % of the incident electric field was reflected from the product. Control using the product temperature was

considered to be preferable since during preliminary trials it was observed that the E-field tended to fluctuate in an apparently random manner whereas the temperature increased more steadily and with greater reproducibility. Agitation of the granules during drying can be used to prevent caking of the bed, but intense or prolonged agitation could result in excessive granule attrition. Hence for the drying cycles included in this part of the study, all of which were performed with agitation, impellor speeds and drive cycles were pre-selected (table 6.4) so as to avoid excessive attrition.

Table 6.4 Pre-selected conditions for the different stages for microwave-vacuum drying of granules by both "high" and "low" process types

Drying stage	Maximum E-field (%)	Maximum product temperature (°C)	Main impellor speed (rev min^{-1})	Impellor drive cycle (sec min^{-1})
First	90	40	20	5
Second	90	42	20	10
Third	90	44	20	10

The time before which the pre-selected end-point conditions were attained varied with the procedure chosen (table 6.5). The granule batches from which product was dried by the "high" and "low" techniques are given in table 6.5. Granule drying using the "high" process type was performed on granules from both batches 1 and 2 in order to compensate for possible inter-batch variations.

Table 6.5 Conditions used for microwave - vacuum drying of three lots of wet granules

Granule Batch	1	2	2
Process Type	"High"	"High"	"Low"
Time to reach end point temperature (mins)	57	55	109

6.2.2.8 Radio frequency drying (batch 3)

Radio frequency drying was carried out using a prototype laboratory scale drier operated at 27.12 MHz, the main features of which are shown in figure 6.2. The wet weight of the sample of granules dried was 0.8 kg. The sample of granules were housed in a PTFE container. Perforated screens were used for the lid and the base of the container to allow the granule bed to be purged with filtered air preheated to 35°C, the purpose of which was to remove evaporated water from the granule bed. The granule container was placed into the drying chamber which was connected the wet mass to a 6.5 kW generator via perforated electrodes situated above and below the granules (Rosefair Electronics Ltd., Watford, U.K.). During preliminary trials, the distance between the two electrodes was adjusted or "tuned" in order to achieve a similar frequency of waves propagating through the material as that produced by the generator. Granules were initially dried using a power corresponding to approximately 6.3 kW. During the first 3 minutes of drying it was necessary to periodically re-tune the radio frequency generator to maintain the drying power as close as possible to 6.3 kW. After this time the power supplied to the granules was allowed to decrease as moisture was removed. When the power output had decreased to approximately 0.5 kW the generator was switched off and the granules removed from the container. The loss in moisture as a result of this radio frequency drying procedure was approximately 34 $\%^{w}/_{w}$ on a dry weight basis. Granules dried using the above conditions appeared slightly damp. Drying was completed under ambient conditions after which the loss in moisture on a dry weight basis was approximately 36 $\%^{w}/_{w}$.

6.2.3 Physico - mechanical characterisation of dried granules

Dried granules were passed through a screen with an aperture diameter of 1.7 mm (10 mesh) and equilibrated under ambient conditions (approximately 10°C at 30% relative humidity) for a minimum of 15 hours prior to testing.

Samples of a suitable size for sieving were obtained from the bulk granules using a riffling sample divider. Granules were sieved and their size distributions determined using the method described in section 2.2.1 except that in addition to sieves having nominal aperture diameters of 180 µm, 90 µm, 75 µm, 63 µm, and 45 µm, sieves with diameters of 250 µm, 355 µm and 500 µm were used. It is

recognised that use of such a large number of sieves may result in poor sieving efficiency. However, all granule samples contained few particles with sieve diameters greater than 180 μm and thus the bulk of the granules passed through the first first four sieves rapidly. In an attempt to eliminate possible effects caused by differences in granule size distribution between the variously dried granules on the subsequent physico-mechanical characteristics (section 5.3), sieve fractions were recombined according to the formula presented in table 6.6 providing samples with standardised size distributions.

Table 6.6 Formula for preparation of size standardised granules following drying by various techniques

Sieve diameter (μm)	Percentage of particles (weight basis)
355 - 500	1.250
250 - 355	1.250
180 - 250	1.875
90 - 180	15.625
75 - 90	50.000
63 - 75	15.625
45 - 63	9.375
less than 45 μm	5.000

Granule bulk density and flow characteristics, the latter in terms of the coefficient of weight variation of tablets produced, were evaluated using size standardised products by methods described in sections 2.2.6 and 2.2.7 respectively. In addition, granule moisture content following equilibration at a relative humidity of 53 % was determined using the method described in section 9.2 without sample pre-vacuum drying. Powder X-ray diffractograms were obtained using a Philips model APD 3720 powder diffraction system, equipped with a vertical goniometer in the $\theta/2\theta$ geometry. The X-ray generator (type; XRG 31000, Philips) was operated at 45 kV and 40 mA using the copper Ka line at 1.544056 Å as the radiation source. Each sample was scanned between 2 and 32 degrees 2θ and in step sizes of 0.04 degrees 2θ . Philips APD software version 3.00 was used for data collection. The percentage of crystalline material,

%Cr, was determined using the method proposed by Nelson & O'Connor (1964b) and described in section 3.2.5. The specific surface area (methods A and B) and intragranular porosity and pore size distribution of variously dried granules were evaluated according to the methods described in sections 2.2.3 and 2.2.4 respectively.

Size standardised granules were compacted and the mechanical properties of tablets determined using the methods described in sections 2.2.8 and 2.2.9 respectively. In addition to visual comparison of tablet tensile strength / corrected work of failure - upper punch force profiles, using Genstat 5 a statistical technique was performed on the curves in pairs to ascertain if the two curves under test were significantly different. The analysis method comprised of fitting a single curve through the combined sets of data for the two curves. This provided a model for the combined sets of data. A factor was added to this model in order to fit a new model which incorporated separate parameters for the data for each of the original curves. The significance of the improvement in the model was assessed by examining the F - ratio at the 95 % level for the change in the regression sums of squares.

Tablet disintegration times were determined using the method described in the USP XXI except that individual disintegration times for each of six tablets were determined. Distilled water maintained at 37°C was used in the tests. In the case of tablets prepared from differently dried granules, the test was performed on tablets compacted at an upper punch force of 15.2 ± 0.4 kN. However, for tablets prepared from ungranulated MCC, tablets compacted at various upper punch forces were tested. The mean disintegration times for 6 tablet lots was determined. The apparent tablet relative densities were calculated from the thickness, diameter and weight of ten individual tablets using a true density value of 1.54 gcm^{-3} (section 2.3.5).

6.3 Results and discussion

6.3.1 Compactibility of variously dried granules

The compaction profiles for granules prepared from wet mass batch 1 and dried by various techniques, together with the profiles for ungranulated MCC are shown in figures 6.3 and 6.4. From the profiles it can been seen that wet granulation resulted in a decrease in compactibility of MCC regardless of the

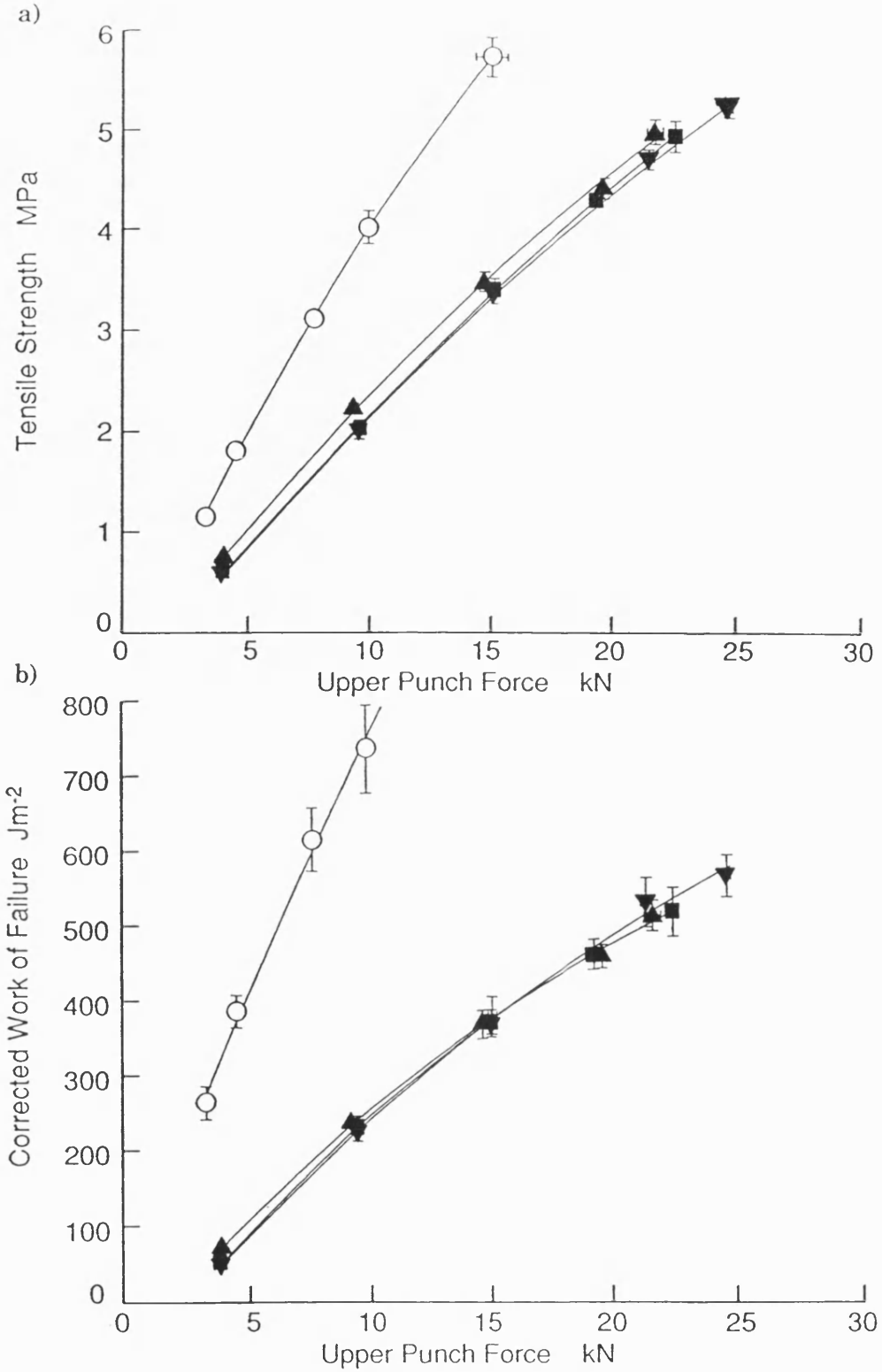


Figure 6.3 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, and from granules tray dried under various conditions. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: ○
Granules: i)Tray dried at 60°C until 'just dry'; ■ ii) Tray dried at 60°C until 'over dry'; ▼ iii) Tray dried under ambient conditions; ▲.

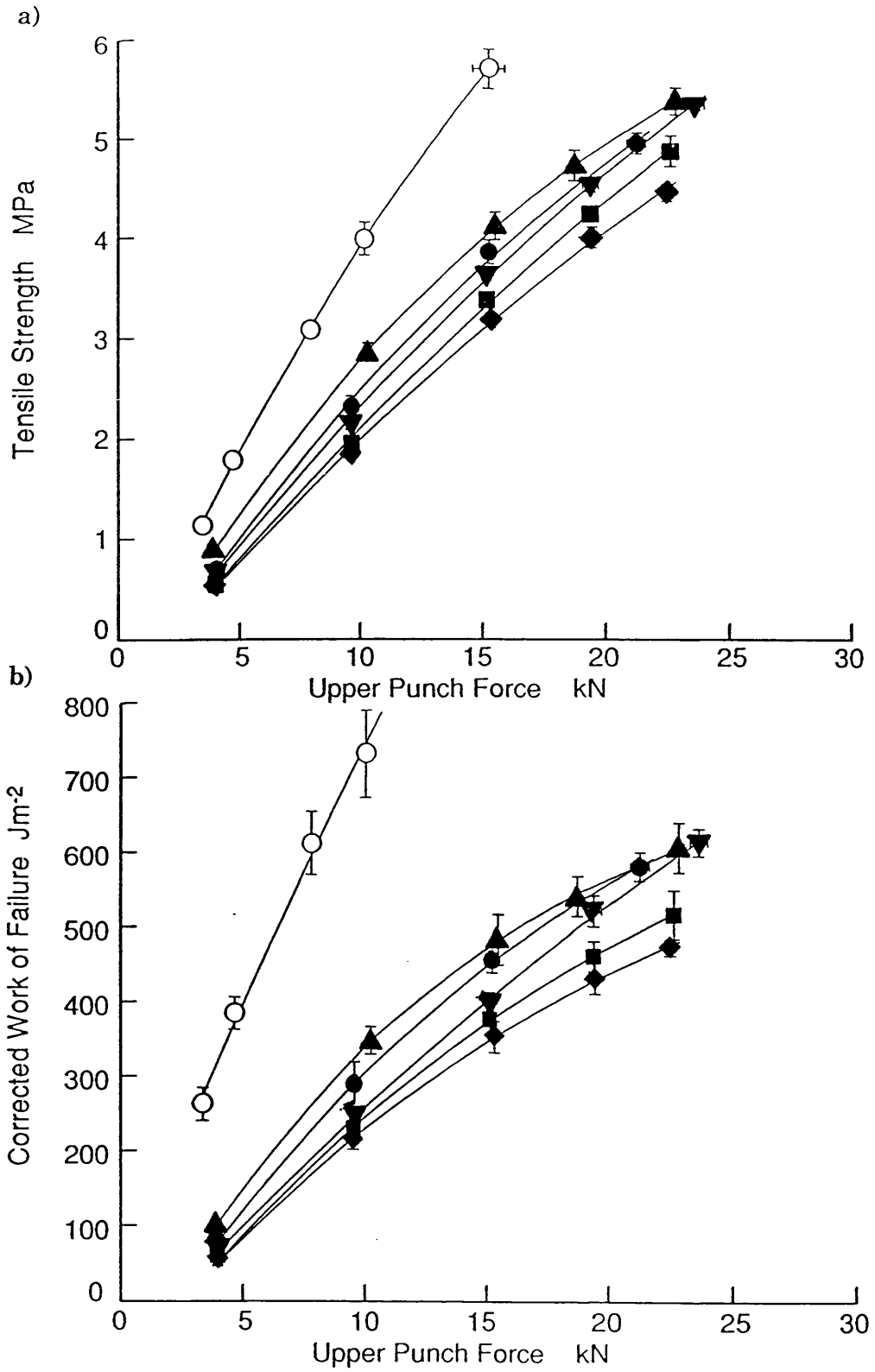


Figure 6.4 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, and from granules dried using various techniques. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: ○
Granules: i) Microwave - vacuum dried ('high' process type); ▲ ii) Freeze dried; ● iii) Fluidised bed dried; ▼ iv) Tray dried until 'just dry'; ■ v) Vacuum dried; ◆

drying method employed. The reduction in compactibility was, however, less than reported in section 3.3.2 for granules prepared with a slightly greater proportion of water (41.2 $\%^{w}/_{w}$) and which were prepared on a smaller scale in a different mixer. This apparent discrepancy is perhaps due to the differences in the proportion of granulation fluid (section 3.3.2) and intensity of granulation (section 4.3). The profiles in figures 6.3 and 6.4 also reveal that some of the drying techniques used can influence the degree of loss in compactibility, discussed in detail below.

The tensile strength - compaction profiles for the tray dried materials dried at 60°C until "just dry" or "over dry" (figure 6.3a) were statistically similar over the entire range of compaction forces used. Visual inspection of the profiles in figure 6.3a also revealed that granules dried under ambient conditions produced tablets of a similar strength to those dried by the two oven tray drying methods at 60°C, particularly when prepared at an upper punch force of 15 kN or greater. In addition, the work of failure - compaction force profiles for granules tray dried at 60°C to "just dry" or "over dry", and dried under ambient conditions were statistically similar over the range of compaction force studied (figure 6.3b). Thus, although the rate and temperature of drying may affect the degree of hornification of cellulose fibres (Giertz, 1961: Treiber & Abrahamson, 1972), results of the present study show that with respect to convective tray drying, over drying in comparison to drying to 'just dry' conditions, and drying at 60°C in comparison with ambient temperatures had an insignificant effect on the strength and toughness of tablets produced.

The statistical analysis employed indicated that with the exceptions described immediately above, the profiles for tensile strength and work of failure as a function of compaction force for tablets produced from the differently dried granules from batch 1 were significantly different from each other. Nevertheless, although perhaps statistically different, visual assessment of some pairs of profiles suggested little difference of practical importance between the samples in question. Where a discrepancy arose between statistical and visual assessments, this was considered to be due to variations in the magnitude of differences between profiles under consideration over the range of compaction forces used. Visual assessment of compaction profiles was considered to provide a better comparison between profiles, and is therefore used in the discussion below.

Tablets prepared at compaction forces below approximately 12 kN from granules dried by microwave-vacuum drying using the "high" process type exhibited superior compactibility in comparison with granules dried by the other techniques (figure 6.4). At higher compaction forces the strength and toughness of tablets produced following microwave-vacuum drying was generally comparable with tablets prepared from freeze dried and fluidised bed dried granules (figure 6.4). Granules having the second highest overall compactibility were freeze dried granules followed by fluidised bed dried granules (figure 6.4). Although tablet strengths were similar to those produced using fluidised bed drying, freeze drying of granules yielded tablets with higher toughness, particularly at compaction forces below approximately 17 kN. Tray dried granules, represented in figure 6.4 by the profiles for tablets prepared from granules dried at 60°C until "just dry", produced tablets with inferior tensile strength to those fluidised bed dried over the compaction force range studied, and with inferior toughness when compacted at forces above approximately 15 kN. Vacuum dried granules exhibited the lowest overall compactibility, producing tablets of a slightly lower strength and toughness than tray dried granules (figure 6.4). It should be noted that although the differences found between adjacent profiles in figure 6.4 were in most cases small, in some instances appreciable differences may be observed between non-adjacent profiles. For example, if it was required to produce tablets having a tensile strength of 3 MPa then a compaction force of approximately 14 kN would be necessary when using tray dried granules compared to 11 kN for microwave-vacuum dried granules.

Granule drying by the "low" microwave-vacuum drying process resulted in tablets with inferior strength and toughness over the entire compaction force range studied in comparison with granules dried by the "high" microwave-vacuum process type (figure 6.5). Thus, in contrast to tray drying using a temperature of 60°C or under ambient conditions, factors related to the rate of drying by the microwave-vacuum appear to have an influence on subsequent granule compactibility. The profiles in figure 6.6 suggest that radio frequency drying of granules resulted in tablets with perhaps slightly reduced tensile strengths but comparable work of failure values in comparison with tablets prepared from tray dried granules from the same wet granule batch.

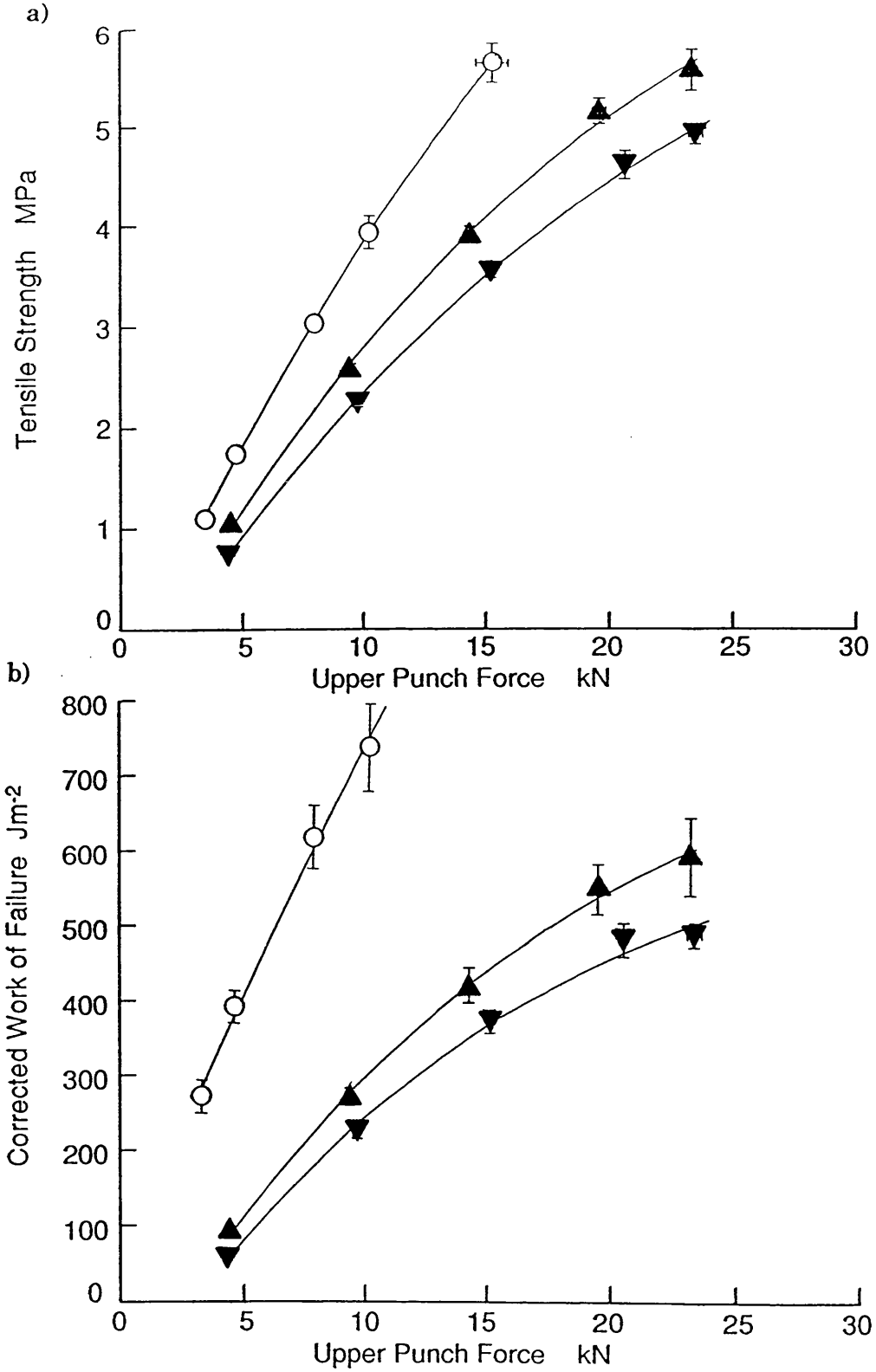


Figure 6.5 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, and from microwave - vacuum dried granules dried using differing conditions. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: ○
Granules: i) Microwave - vacuum dried by the 'high' process type; ▲
ii) Microwave - vacuum dried by the 'low' process type; ▼

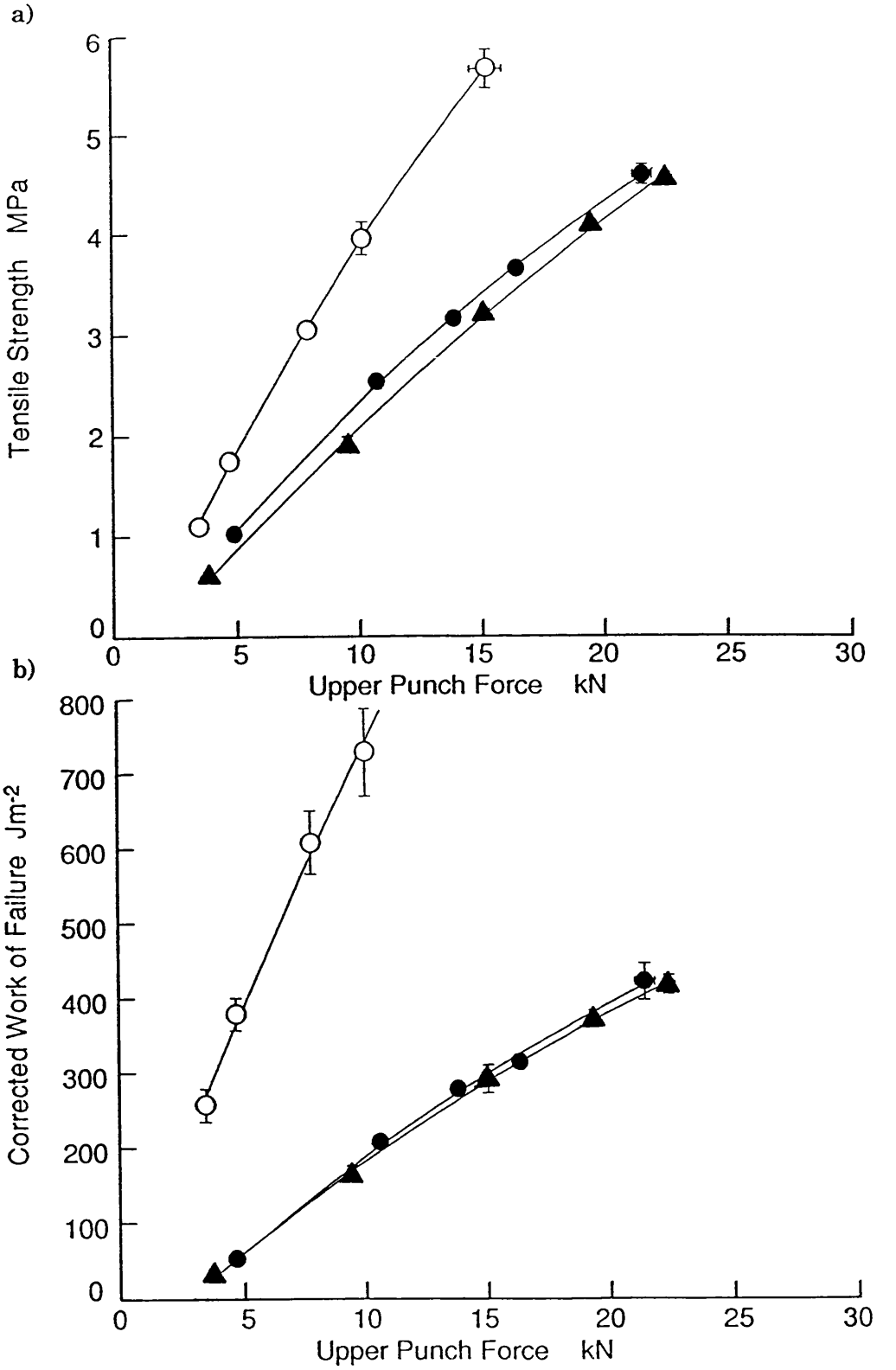


Figure 6.6 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, and from tray dried and radio frequency dried granules.
Key: Ungranulated MCC: ○
Granules: i) Tray dried until 'just dry'; ● ii) Radio frequency dried; ▲

6.3.2 Influence of drying technique on granule particle size distribution, bulk density and flow characteristics

As reported in section 5.3, wet granulation of MCC in the absence of dissolved binders resulted in a modest increase in the mean particle size of dried granules in comparison with ungranulated MCC powder (table 6.7). The resulting granule size distribution was, however, found to vary with the drying technique employed. For granules dried from batch 1, drying techniques involving some degree of agitation (fluidised bed and microwave-vacuum drying) tended to produce smaller granules than other, static bed, drying techniques (table 6.7). Although involving a continuous throughflow of air, radio frequency drying occurred from a static bed and did not result in excessive granule attrition (table 6.7).

Regardless of the drying method employed, granulation resulted in an increase in the poured and tapped bulk densities and an improvement in the flow characteristics of MCC (table 6.7). Although size standardised, the bulk densities of granules were found to vary with the drying technique employed (table 6.7). In particular, fluidised bed and microwave-vacuum drying resulted in granules with relatively high poured and tapped bulk densities in comparison with granules dried by other techniques. However, such differences were not apparent in the tablet weight variation (table 6.7). A reduction in wet batch size and / or storage of the wet mass for 20 hours prior to drying resulted in an increase in the bulk density for tray dried granules (table 6.7). A similar effect was reported in section 4.3 for wet mass storage for 24 hours before drying.

Comparison of different compaction profiles (figures 6.3 to 6.6 inclusive and discussed above) with bulk density data presented in table 6.7 appears to indicate that no relationship exists between granule compactibility and bulk density. This is in contrast to the results reported in section 3.3 where it was found that, in general, treatments resulting in the production of granules which had a low poured and tapped bulk density together with a high surface area and high porosity also resulted in granules with a compactibility. In section 3.3 it was suggested that reducing the degree of intragranule bonding (section 3.4.1) resulted in improved compactibility. The results of the present investigation suggest that bulk density is not sensitive as a predictor for granule compactibility. Differences

Table 6.7. The effect of granulation and drying method on the particle size distribution, bulk density and flow characteristics of microcrystalline cellulose

Drying method	Wet mass batch	Particle diameters from cumulativepercentage over-size plots (μm)			Size standardised MCC granules		
					Bulk Density (g cm-3)		Flowability
		Median	Upper Quartile Point	Lower Quartile Point	Poured	Tapped	Coefficient of tablet weight var.(%)
Ungranulated Emcocel (as received)	---	55	80	30	0.28	0.40	4.10 (with vibration)
Tray dried "just dry"	1	85	115	70	0.33	0.45	0.51
Tray dried "over dry"	1	85	100	60	0.33	0.44	0.45
Ambient conditions	1	80	100	65	0.33	0.45	0.71
Vacuum dried	1	85	115	70	0.32	0.45	0.37
Fluidised bed dried	1	65	80	50	0.38	0.50	0.78
Freeze dried	1	80	90	60	0.32	0.45	0.55
Microwave -vacuum dried ("high" process type)	1	65	80	40	0.38	0.51	0.50
Tray dried "just dry"	3	90	115	75	0.37	0.50	0.47
Radio frequency dried	3	80	90	60	0.39	0.52	0.42

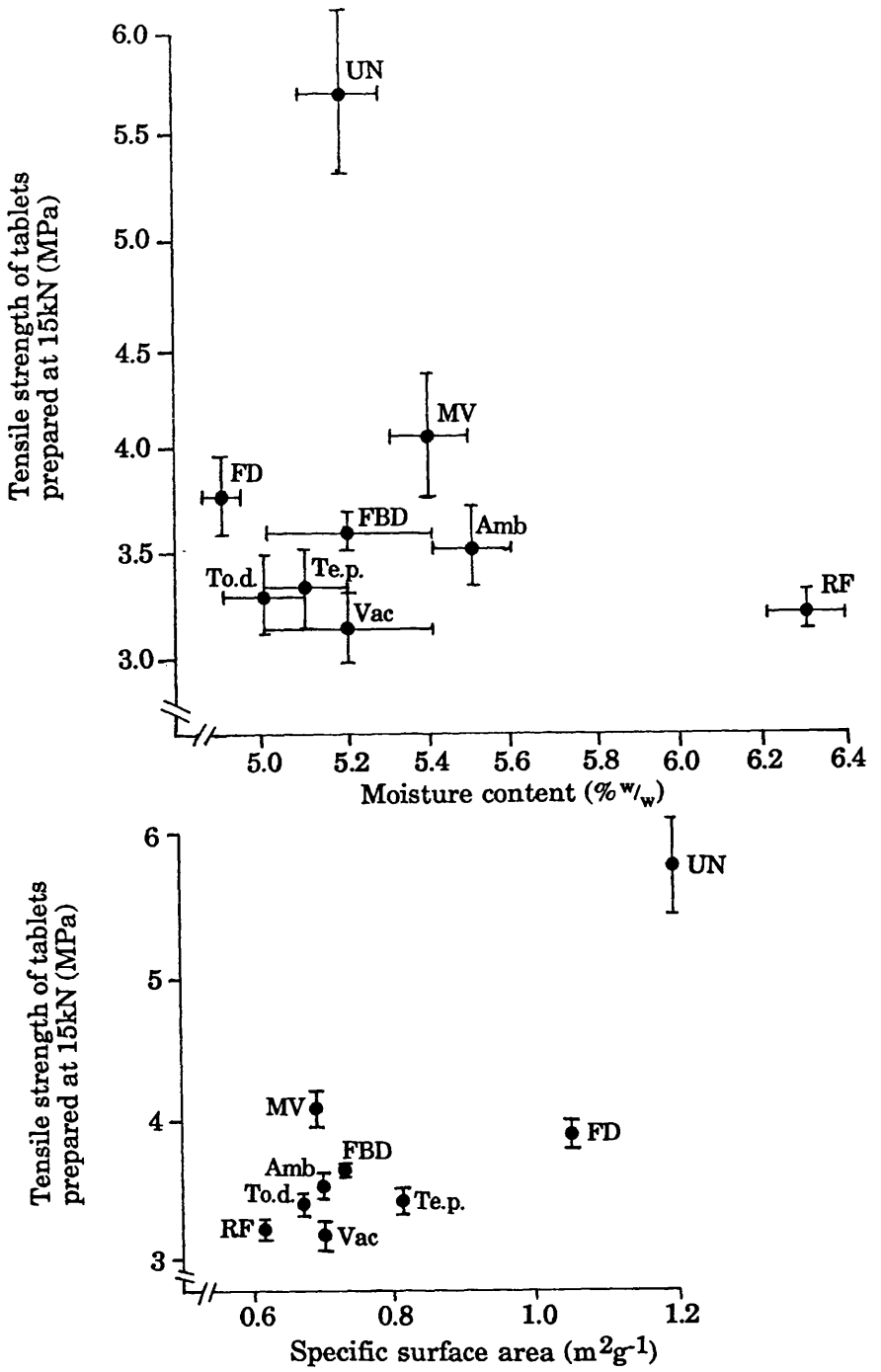
found in the present investigation between the bulk density of variously dried granules may arise from differences in granule porosity caused by different drying mechanisms (6.3.6 below), but may also be influenced by characteristics such as particle shape and surface properties.

6.3.3 Moisture content

It has been reported elsewhere that the compactibility of MCC generally increases with increasing moisture content, the moisture content varied by storage at differing humidities (section 1.5.4.5). It was therefore considered possible that the various drying techniques might result in differences between the physico-mechanical characteristics of granules by simply affecting the granule moisture contents through variable effects on the moisture absorbing capability of granules. For this reason, the relationship between the equilibrium moisture content of MCC granules following storage at a relative humidity of 53%, and the tensile strength of tablets produced at a range of forces was studied; the results are shown in figure 6.7 for tablets produced at 15 kN. The equilibrium moisture content of granules was found to vary with the drying technique employed (figure 6.7). However, it was concluded that no clear relationship existed between moisture content and tablet strength for granules dried in the present study (figure 6.7). Although the data are not presented here, moisture content was not found to be related to the tensile strength of tablets and dried granule type at other compaction forces, nor was there a relationship between moisture content and tablet work of failure. Thus, differences in the compactibility of the variously dried granules cannot solely be attributed to differences in the abilities of the granules to absorb moisture following drying, although such differences may be a contributory factor.

6.3.4 Degree of crystallinity

The X-ray diffractogram for ungranulated MCC is shown in figure 11.2. Although not shown here, the shape of the diffractograms for granulated cellulose products following drying by different drying methods were found to be similar to that for ungranulated MCC. This indicated that the polymorphic form of MCC, which corresponds to that found in cellulose I (native cellulose), was not substantially altered as a result of granulation or drying (discussed further in section 11.4.2.5). Furthermore, no significant difference was found between the percentage of crystalline material in various cellulose granules and ungranulated



Figures 6.7 and 6.8.Relationship between the moisture content (figure 6.7) and specific surface area (figure 6.8) of ungranulated MCC and MCC granules dried using various techniques and the strength of tablets produced at an upper punch force of 15 kN. Note: Error bars around individual data points represent 95% confidence limits.

Key: Ungranulated MCC; UN

Granules; Tray dried ('just dry'); Te.p.
Tray dried ('over dry'); To.d.
Dried under ambient conditions; Amb
Vacuum dried; Vac
Fluidised bed dried; FBD
Freeze dried; FD
Microwave - vacuum dried ('high' process type); MV
Radio frequency dried; RF

MCC (table 6.8). The present results show that the drying technique employed does not affect granule compactibility by altering the polymorphic form or the degree of order in MCC.

Table 6.8 Effect of drying technique on the percentage of crystalline material in wet granulated MCC compared with ungranulated MCC

Drying Method	Percentage of crystalline material
Ungranulated Emcocel (as received)	87
Tray dried, "just dry"	85
Tray dried, "over dried"	87
Ambient conditions	86
Vacuum dried	87
Fluidised bed dried	86
Freeze dried	87
Microwave-vacuum dried ("high" process type)	88
Radio frequency dried	88

6.3.5 Specific surface area

Pesonen & Paronen (1990) have reported a direct, although non-linear, relationship between the particle surface area and tablet strength for four directly compressed cellulosic excipients. Figure 6.8 shows the relationship between the strength of tablets compacted at an upper punch force of 15.0 kN and the B.E.T. specific surface area of the starting powder or granules determined using method A described in section 2.2.3. From figure 6.8 it can be seen that in addition to a reduction in tablet strength, wet granulation resulted in a reduction in the particle specific surface area. In other parts of the present study it was suggested that a reduction in surface area on granulation was unlikely to be solely a result of the increase in particle size (section 3.3.1.4).

For differently dried granules, no clear correlation was found between

granule specific surface area and strength of tablets produced (figure 6.8). Similarly, although not presented here, no correlation existed between surface area and the strength or toughness of tablets prepared at other compaction forces. Although freeze dried granules exhibited a higher specific surface area than other granule types including microwave-vacuum dried granules, the compactibility of freeze dried granules was lower than that of microwave-vacuum dried granules. If the relationship of Pesonen & Paronen (1990) found for ungranulated MCC held for dried granules, from the data for specific surface area freeze drying would have been expected to produce higher tablet strengths than microwave-vacuum dried granules. Specific surface areas determined by method B (section 2.2.3) for a selection of granules are presented in table 6.9 and confirm that freeze drying resulted in the formation of granules with a higher specific surface area in comparison with the other drying techniques. Thus, the relationship of Pesonen and Paronen (1990) does not appear to be universal for all cellulosic materials. The effect of freeze drying on granule surface area is discussed further in section 6.4 below. It was also noted that in comparison with drying under ambient conditions, tray drying at 60°C did not result in reduced granule surface area. Merchant (1957) reported that for water soaked fibres of cellulose which had been dewatered by water - alcohol - hydrocarbon exchange, drying temperatures above 60°C resulted in a progressive decrease in surface area. This was attributed to an increased ability for structural units of fibres to hydrogen bond with adjacent units due to thermal activation at the higher temperatures, a phenomenon not apparent in the present investigation.

Table 6.9. The specific surface areas (method B, section 2.2.3) for size standardised granules dried by various techniques

Drying method	Specific surface area (m^2g^{-1})
Freeze dried	1.07
Microwave-vacuum dried (high process type)	0.66
Fluidised bed dried	0.60
Tray dried "just dry"	0.54

6.3.6 Porosity

The pore size distributions for microwave-vacuum dried granules dried by the "high" process type, freeze dried granules, and for tray dried granules are presented in figure 6.9. Using the criterion that pores with a diameter less than 10 μm are intraparticle pores, the pore size distributions show no evidence of substantial differences between the intragranular porosity of these three granule types. However, the calculated intragranular porosity of the three granule types had a similar rank order to their relative compactibilities (table 6.10). Thus, granule porosity may provide an indication of the deformability of these dried granules. In addition, it was noted that granulation resulted in a reduction in the intraparticle porosity regardless of the drying technique employed (figure 6.9 and table 6.10), the effect of granulation on reducing intraparticle porosity consistent with the findings discussed in section 3.3.1.3.

Table 6.10. Relationship between intraparticle porosity of ungranulated MCC and for granules dried using a variety of techniques with strength of tablets produced

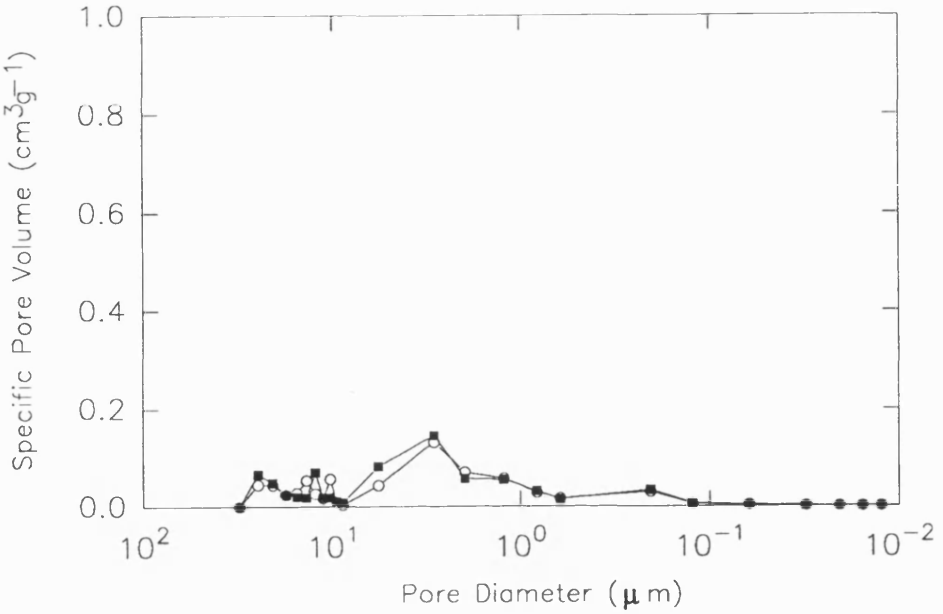
Granule drying technique	Total intraparticle porosity cm^3g^{-1}	Tensile strength of tablets produced at an upper punch force of 15 kN (MPa)
Ungranulated MCC	0.42, 0.48	5.7
Microwave-vacuum dried "high" process type	0.35	4.1
Freeze dried	0.30	3.9
Tray dried to "just dry"	0.27	3.5

6.3.7 Disintegration times

In the case of tablets prepared from dried granulated MCC, disintegration times were found to be related to tablet tensile strength and toughness, and may therefore be independent of the drying process employed (table 6.11). However, the disintegration times did not appear to be related to the tablet relative densities (table 6.11). This suggests that the disintegration time was dependent on the bond strength rather than on the total pore volume within tablets. Interestingly, although

Figure 6.9 Pore size distributions of ungranulated MCC and MCC granules dried using various techniques.

a. Duplicates of pore size distributions for ungranulated MCC.



b. Pore size distribution of microwave - vacuum dried granules (dried by the 'high' process type)

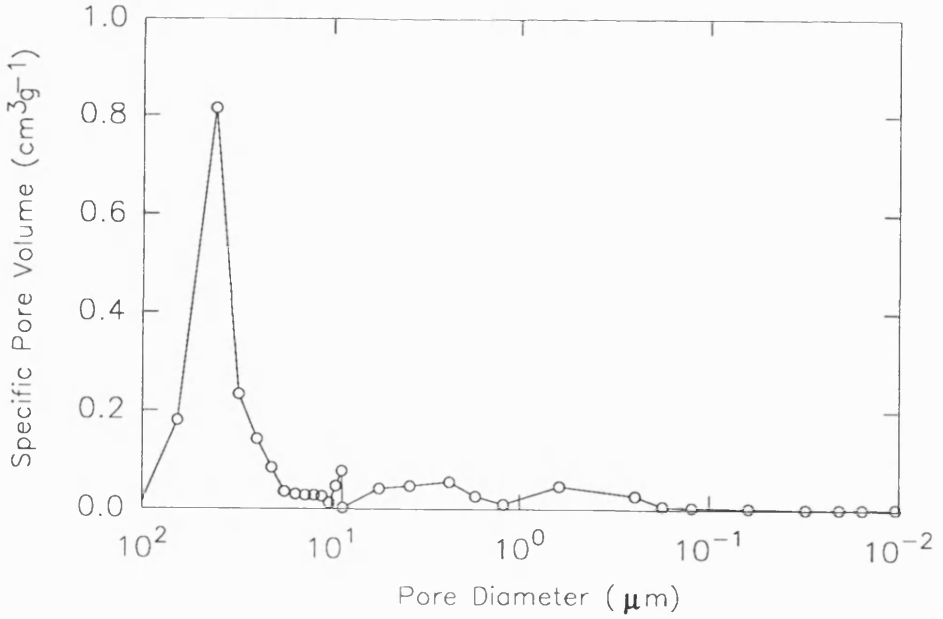
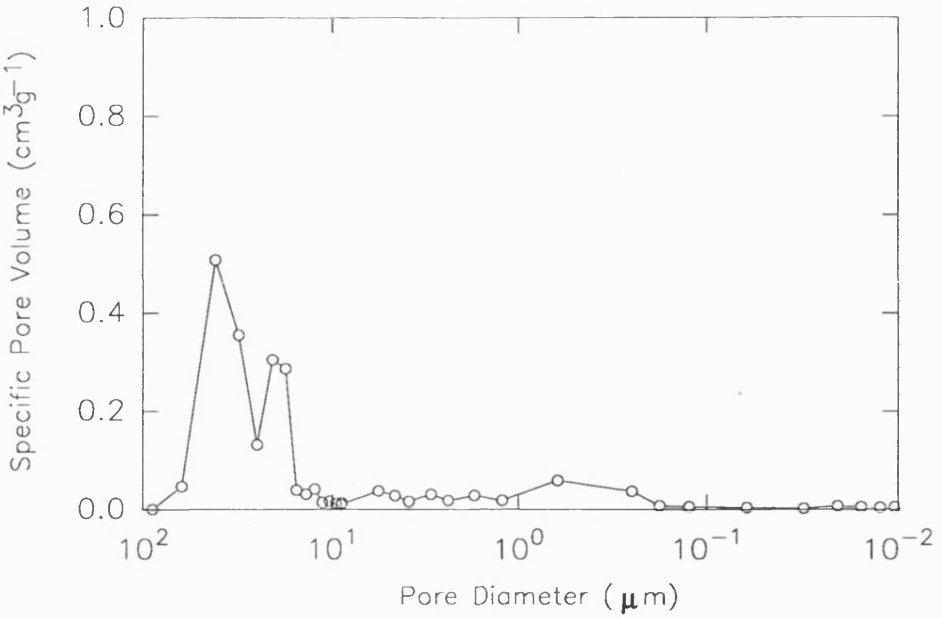
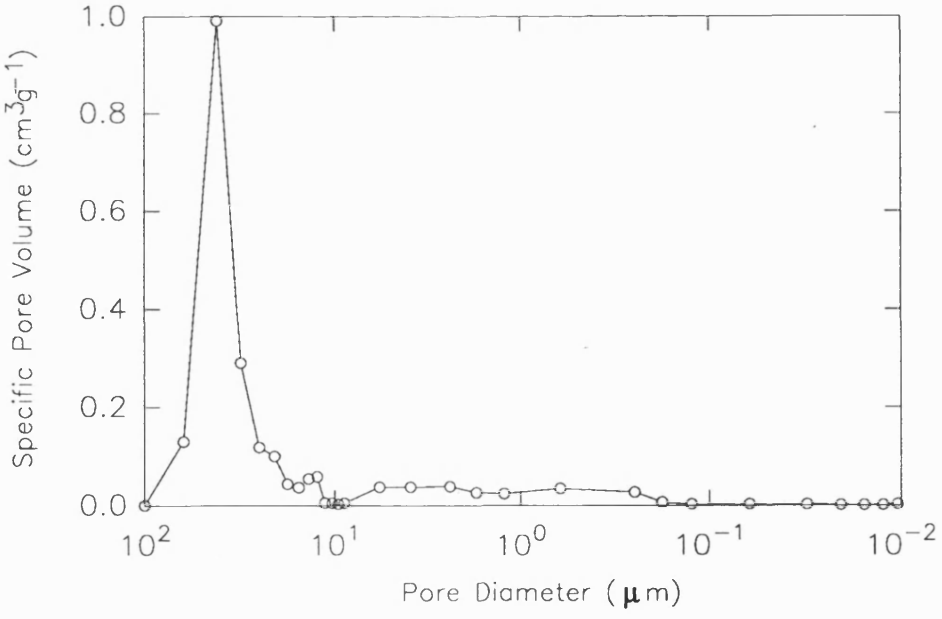


Figure 6.9 (continued)

c. Pore size distribution of freeze dried granules



d. Pore size distribution of tray dried granules (dried until 'just dry')



tablets prepared from ungranulated MCC at an upper punch force of 10.1 kN were found to have comparable strength to tablets prepared from granules compressed at 15 kN, the former tablets exhibited much longer disintegration times than the latter (table 6.11). However, tablets prepared from ungranulated MCC at an upper punch force of 4.7 kN, which had comparable toughness to tablets prepared from MCC granules at 15 kN, exhibited disintegration times of a similar order of magnitude to tablets compressed from MCC granules. Thus, disintegration times for ungranulated and granulated MCC tablets are, in general, related to tablet toughness rather than tablet strength.

6.4 Discussion of the effects of drying technique on the physico-mechanical characteristics of MCC granules

In section 3.4.1 it was suggested that in the case of tray drying, wet granulation of MCC in the absence of a dissolved binder results in increased intraparticle bonding caused by surface tension of the menisci in the drying front drawing microcrystals together. This may result in a reduction in the deformability of the excipient, and less interparticle bonding produced on compaction and resulting in weaker tablets.

As discussed in section 1.2, the use of various drier types and selection of different drying process variables may result in alterations in the rate and mechanisms by which heat and mass transfer occur during the drying procedure, and therefore may promote differences in the final product characteristics. Studies concerning the effect of drying technique on the micromeritic and compaction characteristics of wet granulated materials have been largely confined to formulations containing dissolved solids or binders (discussed in section 1.2). Few studies have been reported concerning the comparative effects of drying technique on the physico-chemical properties of insoluble excipients such as MCC in the absence of dissolved materials. However, as discussed in section 1.5.3, it has been noted, although without the presentation of experimental evidence, that tray drying of cellulose microcrystals results in the production of a material with inferior compaction properties to the spray dried product, and that freeze drying results in the formation of a very "light" powder (Battista & Smith, 1962).

During dielectric drying, the rate of evaporation of moisture from the granule interior may exceed that from the surface resulting in boiling of the water

Table 6.11. Disintegration times for tablets prepared from ungranulated and granulated MCC, with 95% confidence limits

Drying method / material	Wet mass batch	Compaction force (kN)	Tablet tensile strength (MPa)	Tablet work of failure ($J\ m^{-2}$)	Tablet relative density	Disintegration Time (sec)
Ungranulated MCC	---	15.1 ± 0.12	5.8 ± 0.21	1060 ± 105	0.85	330 ± 30
	---	10.8 ± 0.06	4.1 ± 0.14	744 ± 52	0.79	210 ± 26
	---	4.9 ± 0.03	1.8 ± 0.08	392 ± 21	0.66	80 ± 10
Granules:						
Microwave-vacuum dried, "high" process type	1	15.1 ± 0.03	4.1 ± 0.15	480 ± 42	0.85	79 ± 6
Freeze dried	1	15.1 ± 0.04	3.9 ± 0.11	464 ± 21	0.85	70 ± 9
Fluidised bed dried	1	15.0 ± 0.04	3.7 ± 0.05	402 ± 17	0.85	52 ± 7
Ambient conditions	1	15.0 ± 0.05	3.6 ± 0.10	374 ± 20	0.86	45 ± 8
Tray dried, "just dry"	1	15.1 ± 0.04	3.5 ± 0.10	386 ± 16	0.84	54 ± 5
Tray dried, "over dried"	1	15.1 ± 0.05	3.4 ± 0.08	375 ± 24	0.84	39 ± 3
Vacuum dried	1	15.1 ± 0.03	3.2 ± 0.12	360 ± 22	0.84	38 ± 4
Radio frequency dried	3	15.0 ± 0.04	3.2 ± 0.07	299 ± 21	0.86	34 ± 4

inside the granules leading to "puffing" or "explosion" of the product (section 1.2.1 and 1.2.2.2). It is possible that some of the hydrogen bonds formed by surface tension during drying may be disrupted during dielectric drying. Further, if moisture migration occurs by vapour rather than liquid flow in dielectric drying, surface tension effects due to contraction of the menisci between microcrystals would be expected to be lower during dielectric drying in comparison with that occurring during tray dried granules. Both of the above factors might therefore be expected to reduce the amount of intragranular bonding formed during dielectric drying of MCC granules. In the present study, microwave-vacuum drying using the "high" process type was found to result in granules with improved compactibility and higher intragranular porosity as determined using mercury intrusion in comparison with tray dried granules. However, the beneficial effect on compactibility was not observed with microwave-vacuum drying by the "low" process type, nor with radio frequency drying. This suggested that the specific conditions selected for dielectric drying rather than the technique itself may affect the characteristics of the final granule, with increased rate of evaporation of internal moisture perhaps resulting in improved compactibility. Reduced intragranule bonding resulting from microwave-vacuum drying by the "high" process type in comparison with freeze drying was not, however, apparent from measurements of granule specific surface area.

Granule freeze drying was also found to result in improved compaction characteristics in comparison with tray drying. If water in cellulose is frozen and the ice formed is sublimed, there will be no effects from liquid surface tension. Indeed, Merchant (1957) reported that in comparison with conventional drying techniques, freeze drying results in a modest reduction in the degree of irreversible hornification during drying of cellulose pulp, presumed to be for the above reason. However, the specific surface area of dried cellulose pulp was found to increase as the temperature used during either the freezing or drying stages was decreased (Merchant, 1957). In the present study, freeze drying was found to result in only a modest increase in granule surface area and intragranular porosity in comparison with conventional tray dried granules. This is in contrast to results reported in section 7.4 below where drying by solvent exchange was found to increase granule surface area by a greater extent. Considering the results of other workers discussed in section 1.2.2.1, it is suggested here that bound water held in the granule capillaries as a supercooled liquid with a depressed freezing

point caused freeze drying to increase dried granule specific surface area by an amount less than anticipated from theory. The unfrozen moisture would be expected to evaporate from the granules by the same mechanisms prevailing under atmospheric drying at room temperature. This would result in surface tension effects which could potentiate internal collapse of the cellulose granule structure (Merchant, 1957). It is therefore considered likely that alteration of the process variables may allow further improvements in granule compactibility.

The effects of other drying techniques, namely fluidised bed and vacuum drying, on the compactibility of MCC granules in comparison with tray drying are less readily explained. However, it is considered that the poor compactibility of vacuum dried granules may be associated with increased intragranule collapse and therefore intragranular bonding due to the low pressures under which drying was performed. In addition, it is speculated that in comparison with tray drying, granule fluidisation during fluidised bed drying may reduce the length of the moisture migration path through the material. This would also reduce the extent of intragranular collapse due to surface tension effects, thereby improving granule compactibility and increasing granule specific surface area.

Of the drying techniques included in the present study, only microwave-vacuum drying, fluidised bed drying, tray drying, and vacuum drying are currently commercially acceptable for economic reasons. Results suggest that the newly developed method of microwave-vacuum drying, especially using the "high" process type, may offer advantages over other commercially acceptable drying techniques in terms of the subsequent compaction characteristics of aqueous granulations in which MCC is present in significant amounts.

Chapter 7. A study of the effect of dewatering wet granulated MCC by solvent exchange on the physico-mechanical characteristics

7.1 Objectives

The aims of this part of the study were to examine the effect of drying wet granulated MCC by solvent exchange on the physico-mechanical characteristics of the granules produced. In the present study, the term solvent exchange is used to describe the partial or total replacement of water in water-swollen cellulose with a liquid of lower polarity, and drying from that liquid. In addition, the theory that wet granulation of MCC results in quasi-hornification of the excipient, as discussed in section 3.4.1, was examined further.

7.2 Theoretical considerations

Although not shown conclusively, in section 3.4.1 it was proposed that the reduction in compactibility of MCC arising as a result of wet granulation may be partly due to collapse of the granule structure and increased intraparticle bonding. More specifically, it was suggested that shrinkage stresses caused by surface tension effects during removal of water from cellulose fibres by conventional drying methods allowed microcrystals to be brought into sufficiently close proximity to promote extensive intraparticulate hydrogen bonding.

It has been reported elsewhere that the collapse of water-swollen wood fibres (Merchant, 1957; Thode et al, 1958; Stone & Scallen, 1965) and water-swollen MCC (Avicel PH-101) (Nakai et al, 1977b) on drying, as assessed using nitrogen specific surface area analyses, may be prevented or at least reduced reduced by solvent exchange. For example, using solvent exchange, Stone & Scallen (1965) reported that fibres having a nitrogen specific surface area of 230 m^2g^{-1} may be prepared from never-dried fibres, and Merchant (1957) reported that wood fibres with a nitrogen specific surface area of 91.9 m^2g^{-1} may be prepared from previously water-dried fibres. These specific surface areas were in contrast to the much lower values (approximately 1 m^2g^{-1}) reported in the above studies for similar starting fibres dried from water (Merchant, 1957; Stone & Scallen, 1965). Stone & Scallen (1965) suggested that the low surface tension of the exchanging liquid resulted in a relatively small degree of collapse of the

cellulosic structure during drying. However, it has been shown that the extent to which the expanded state is retained following drying by solvent exchange may be greatly influenced by the methodology. In particular, the complete exchange of the water in swollen cellulose with a liquid of low polarity, and evaporation of the final liquid at around 50 - 60°C in the absence of atmospheric moisture favours high final product surface areas (Merchant, 1957; Thode et al, 1958). Complete exchange may be achieved by 1) firstly exchanging the water with a liquid of roughly intermediate polarity such as an alcohol followed by exchanging the alcohol with a solvent of low polarity such as a hydrocarbon, and 2) by forcing the exchanging liquids through the fibres, and 3) by using solvents with low moisture contents. In addition, of several hydrocarbons investigated for water-alcohol-hydrocarbon exchange of cellulose fibres, Merchant (1957) reported that the highest final surface areas were obtained using n-pentane.

Nakai et al (1977b) prepared solvent exchanged MCC by washing water-soaked MCC ten times with absolute ethanol followed by ten washings with n-pentane. Exchanges were performed by shaking a pre-centrifuged quantity of moist cellulose with the exchanging liquid followed by centrifuging the sample and discarding the supernatant. After the final washing, the n-pentane was evaporated from the MCC by vacuum drying. MCC prepared in this way had a specific surface area available to nitrogen of approximately 80 m^2g^{-1}. In contrast, untreated spray dried MCC had a nitrogen surface area of approximately 1 m^2g^{-1}. However, Nakai (1977a) and Hollenbeck et al (1978) reported that the surface area of untreated (spray dried) MCC determined by water vapour adsorption was approximately 150 m^2g^{-1}. This value was greater than the specific surface area available to nitrogen following solvent exchange of water swollen MCC. Hence the solvent exchange method used was only partially successful in preventing collapse of the water-swollen structure. The collapse could have occurred as a result of surface tension forces during evaporation of non-exchanged residual water or due to the surface tension of water present as an impurity in the solvents. In addition, the surface tension, albeit low, of n-pentane may cause some collapse. Plonka (1982), however, obtained MCC with a nitrogen specific surface area of 133.2 m^2g^{-1} by firstly exchanging water in water-swollen MCC with methanol, and then exchanging the alcohol with n-pentane. The higher surface area obtained by Plonka (1982) in comparison with Nakai et al (1977b) may have been due to the higher drying temperatures used by Plonka (1982) to evaporate the n-pentane

and / or because unlike Nakai et al (1977b), Plonka (1982) reported that care was taken to determine surface areas immediately after solvent exchange without exposing the sample to atmospheric moisture. The effect of solvent exchange on the subsequent compaction characteristics of MCC was not, however, reported by either of the aforementioned groups of workers.

Although not solvent exchanged, Millili & Schwartz (1990) investigated the effect of varying the proportion of water to ethanol used as a granulation fluid on the physico-mechanical characteristics of granules and pellets prepared from a mixture of 10% theophylline and 90% MCC. It was reported that pellets became weaker and more friable as the proportion of water in the granulation fluid was decreased. In addition, tablets prepared from pellets granulated with 95% ethanol were stronger than those granulated with water, suggesting alcoholic granulation resulted in improved granule deformability and/or bonding during compaction. Furthermore, as the fraction of water in the granulation fluid was reduced, the pellets became smaller and exhibited lower poured and tapped bulk densities. The authors also reported that similar trends were observed between the physico-mechanical characteristics of unspheronised wet granulated MCC prepared with varying ratios of water to ethanol, although actual data was not presented. However, the effect of varying the granulation fluid was found to be less marked in the case of the simple granulations in comparison with the pellets. No explanation was offered for the differences observed between granules / pellets granulated with varying proportions of water to ethanol.

It was considered that the studies summarised above suggested that intragranular bonding of MCC resulting from wet granulation may be reduced by drying the granules by solvent exchange and further MCC granule compactibility may thereby be improved. Results of such a study are presented below.

7.3 Materials and methods

Granules were prepared batchwise by the general method described in section 3.2.1 using 150 g MCC (Emcocel 50M, lot number 8261, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) and 105 g distilled water which corresponded to 41.2 $\%^{w}/_{w}$ water in the wet mass. Three dewatering techniques were investigated: Firstly, water-alcohol-non polar solvent (WAN) exchange was performed by successively washing 255 g wet massed MCC with methanol five

times, each washing using 300 ml methanol, followed by four washings with n-pentane, each washing using 250 ml pentane. Secondly, water-alcohol (WA) exchanged granules were prepared by washing 255 g wet massed MCC five times with methanol only, each washing using 300 ml methanol. The solvent exchanges were performed in a Buchner funnel and flask. The appropriate amount of solvent was added to the MCC wet mass with thorough stirring for five minutes, after which as much liquid as possible was removed by vacuum filtration. The methanol (ACS reagent grade, 99.9% purity, less than 0.1% moisture, Aldrich Chemicals Ltd., Gillingham, Dorset, batch number 91-119) and n-pentane (spectrophotometric grade, greater than 99% purity, less than 0.01% moisture, Aldrich, batch number 91-029) were used as received. WAN- and WA-exchanged granules were subsequently spread on trays and allowed to dry under ambient conditions (45 % relative humidity, 10-15°C). Thirdly, a control set of non-exchanged wet granules were also dried under ambient conditions.

Sieve separation was performed on dried granules using the method described in section 3.2.2. In an attempt to eliminate possible effects caused by differences in granule size distribution between the variously dried granules on the subsequent physico-mechanical characteristics (section 5.3), sieve fractions were recombined according to the formula presented in table 3.1 providing samples with standardised size distributions. The compactibility of size standardised granules was assessed using the methods described in section 2.2.8 and 2.2.9. All three granulated products had acceptable flow and did not require additional vibration of the feed shoe during compaction to achieve adequate die filling and acceptable uniformity of weight. The surface area for granules with sieve diameters in the range 75 - 90 μm were determined using methods B and C described in section 2.2.3. Bulk densities of size standardised products were determined using the technique described in section 2.2.6. Scanning electron micrographs were obtained for particles with sieve diameters between 90 and 180 μm using the method described in section 2.2.2. Moisture contents following equilibration at a relative humidity of 53 % were determined by the loss on drying technique described in section 9.2 without pre-vacuum drying the samples.

The physico-mechanical characteristics of granules were compared with results obtained for ungranulated MCC. Data for the latter was obtained using material with a size distribution as received except for moisture contents which

were determined using particles in the size range 75 - 90 μm.

7.4 Results

The profiles for tablet tensile strength and work of failure as a function of compaction force for the three differently granulated products and for ungranulated MCC are presented in figure 7.1. Granulation was found to result in a reduction in the compactibility of MCC irrespective of the dewatering technique employed. However, solvent exchange of granules yielded tablets with a significantly higher strength and toughness than conventionally dried granules. Furthermore, WAN-dried granules exhibited superior compactibility in comparison with WA-dried granules.

Differences in compactibility observed between differently prepared granules were also reflected in differences in their physical characteristics (table 7.1). The increased compactibility of granules dewatered by WA- and WAN-drying was associated with higher granule specific surface areas and reduced poured and tapped bulk densities. These trends were generally consistent with those reported in sections 3.4.1 and 4.3. In addition, the dewatering technique employed was found to affect the equilibrium moisture content of dried granules with an increase in granule compactibility associated with an increase in granule moisture content (table 7.1). However, comparison of the physical characteristics of granules dewattered by various techniques with ungranulated MCC suggests only a partial dependence of compactibility on the surface area available to nitrogen and moisture content for MCC materials (table 7.1), since although the compactibility of ungranulated MCC was higher, it exhibited a lower specific surface area and moisture content in comparison with WAN- and WA-dried granules. Further, it should be noted that although the surface area results obtained by method B were lower than obtained by method C (table 7.1), the two methods ranked the MCC materials in a similar order. The poured and packed bulk densities showed a similar rank order with compactibility for all MCC materials although it should be noted that the mean size and size distribution for ungranulated MCC was different to that of the granules. Scanning electron micrographs (figure 7.2) suggested that WA- and WAN-drying produced MCC granules with an intraparticle density which was higher than that of ungranulated MCC, but lower than that for conventionally dried granules. This relationship correlated approximately with compaction data but not with specific surface area

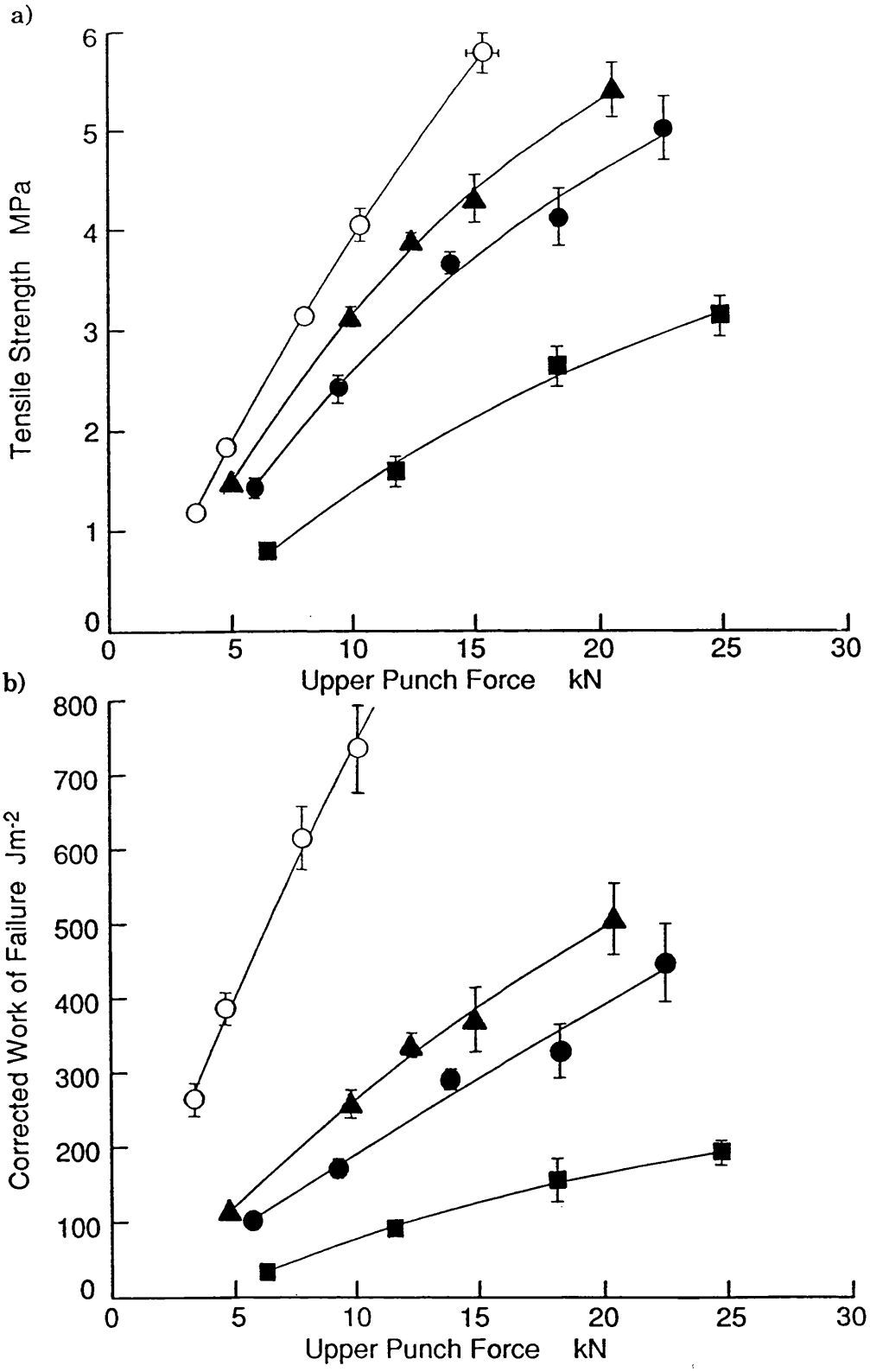


Figure 7.1 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, and from granules dewatered by various techniques. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: ○
Granules: i) Conventionally tray dried granules; ■ ii) Water - methanol exchanged granules; ● iii) Water - methanol - pentane exchanged granules; ▲

Table 7.1 Pysical characteristics of wet granulated MCC dewatered using three different techniques (values for ungranulated MCC are given for comparison)

	Moisture content ($\%^{w}/_{w}$)	Specific surface area (m^2g^{-1})		Bulk density (gcm^{-3})	
		Method B	Method C	Poured	Tapped
WAN-dried granules	7.0	2.1	2.4, 2.3	0.34	0.43
WA-dried granules	6.7	1.7	---	0.37	0.47
Conventionally dried granules	6.6	0.41, 0.40	1.02, 1.04	0.40	0.50
Ungranulated MCC	6.5	1.29, 1.28	1.76, 1.69 1.58, 1.58	0.25	0.36

Table 7.2. A summary of particle size characteristics of ungranulated MCC and granules dewatered by three different methods in sieve fractions between 75 and 250 µm

Sieve size fraction	Percentage of particles by weight			
	WAN-dried granules	WA-dried granules	Conventionally dried granules	Unngranulated MCC
75 - 90 µm	15.7	14.3	14.8	29.4
90 - 180 µm	35.6	43.6	53.9	9.6
180 - 250 µm	10.5	14.5	19.6	0
Cumulative percentage of particles in the size range 75 - 250 µm	61.8	72.4	88.3	39.0

Figure 7.2 Scanning electron photomicrographs of ungranulated MCC and MCC granules dewatered using various techniques (Note: column I shows a general view of groups of particles at a lower magnification, and column II shows details of individual agglomerates).

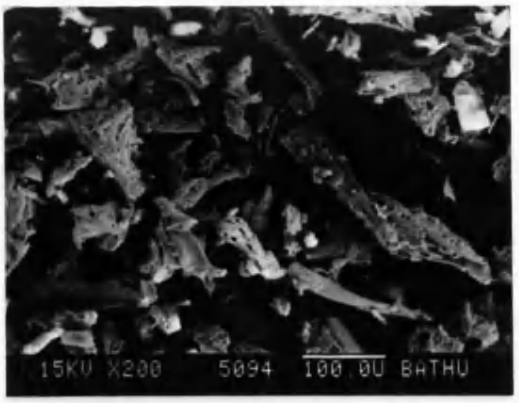
I II

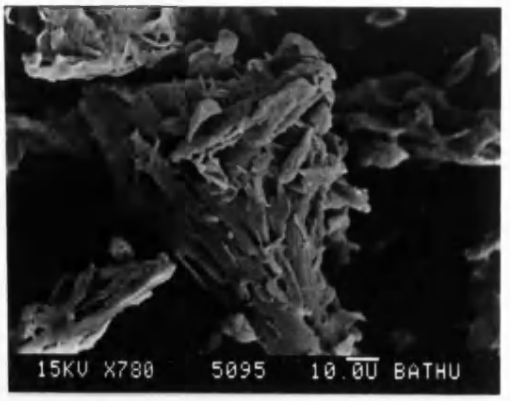
a. Ungranulated MCC

b. Water - methanol exchanged granules

c. Water - methanol - pentane exchanged granules

d. Conventionally tray dried granules


15KV X200 5094 100.0U BATHU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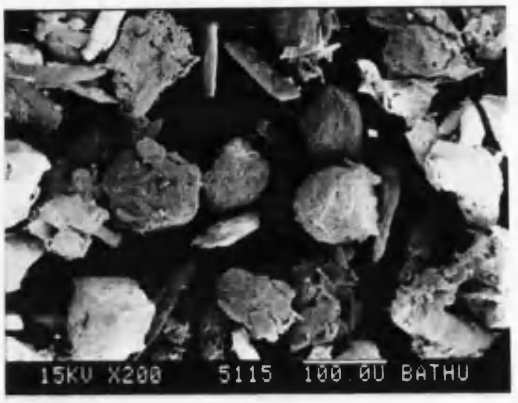
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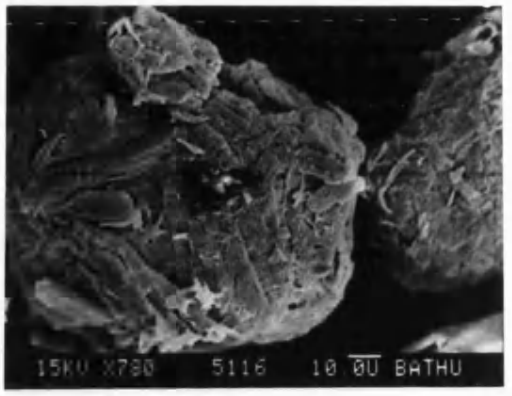
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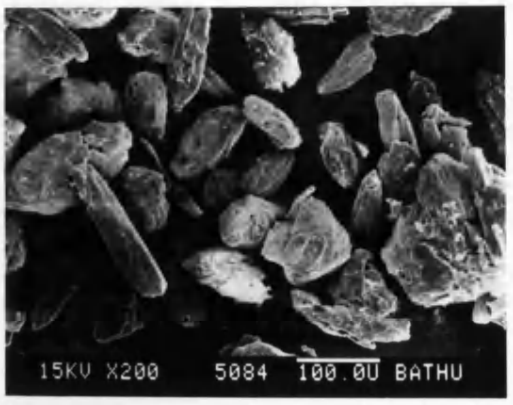
15KV X200 5111 100.0U BATHU


15KV X780 5112 10.0U BATHU


15KV X200 5084 100.0U BATHU


15KV X780 5083 10.0U BATHU

values; the increased specific surface area of WAN- and WA-dried granules over ungranulated MCC was not apparent from scanning electron microscope studies.

Conventional drying resulted in the greatest number of coarse MCC granules having sieve diameters in the range between 75 and 250 μm, followed by WA-drying and WAN-drying. The data presented in table 7.2. is only a summary of particle characteristics and it should be noted that granule drying by any of the three techniques resulted in an increase in the mean particle size in comparison with ungranulated MCC.

7.5 Discussion

In the present study, WAN-dried granules exhibited a higher surface area when compared with WA-dried granules (table 7.1). This difference suggested that WAN-drying was more effective than WA-drying in preventing collapse of the water-swollen structure of wet granules during drying and was anticipated from results obtained by Merchant (1957) and Stone & Scallen (1965). However, the surface area of WAN-dried granules was 2.1 m^2g^{-1} which is substantially lower than the specific surface area of ungranulated and granulated MCC available to water vapour (106.5 and 105.1 m^2g^{-1} respectively) reported in section 10.3.4 below. This suggested that the WAN-drying technique used in the present study did not substantially prevent collapse of the previously water-swollen structure, although granules were less collapsed than when dried by conventional means. The poor efficiency of the WAN-drying technique is perhaps not surprising when the methodology is considered; the solvents used were not predried and exchanging was performed under ambient humidity conditions and by gentle stirring rather than by flowing the solvents through the cellulosic material, and evaporation of the final solvent was performed under ambient humidity. Other workers have suggested that these factors would not favour retention of the swollen structure in the dried state (Merchant, 1957; Thode et al, 1958). Thus, it may be expected that residual water and methanol may be retained in the cellulose, which upon drying would cause collapse of the granules. Similarly, the WA-drying technique was less effective than may have been achievable using a higher degree of control over moisture present in the alcohol and the environment, and higher solvent evaporation temperatures.

Despite the modest increase in surface areas in comparison with conventional dried granules, the improvement in compactibility following WA and

WAN-drying was marked (figure 7.1). It was considered that the improvement in granule compactibility resulting from drying by solvent exchange could be a result of a reduction in intragranule collapse and thus the formation of less highly bonded granules which have greater ability to deform during compaction. Although the higher surface area indicated a less internally bonded structure within the WAN and WA-dried granules in comparison with ungranulated MCC, WAN and WA-dried granules exhibited inferior compactibility in comparison with ungranulated material. Thus, despite spray drying of MCC causing collapse of the structure (although less than may occur following wet granulation) the spray dried product exhibited improved deformation or bonding characteristics in comparison with WAN- and WA-dried material. The reasons for this are unclear, but may be due to residual solvents, discussed immediately below, in the WAN- and WA-dried granules which may inhibit inter-particle bonding within tablets.

Merchant (1957) reported that solvent exchange of cellulose fibres generally results in some residual solvent(s) remaining in the final product even if the cellulose is heated above the boiling point of the solvent. The mechanism by which residual solvents were retained was discussed by Merchant (1957). He proposed that the surface tension during drying from solvent, albeit reduced, may still lead to collapse of pores in which traces of solvent may be trapped. The presence of residual solvents in the granules and their effect on physico-mechanical characteristics of granules was not investigated in the present study. However, their occurrence was considered likely from consideration of the discussion presented by Merchant (1957).

The reason for the relatively high moisture contents of the WA- and WAN-dried granules is also unclear. The ability of water to penetrate the structure of granules should result in the moisture absorbing capabilites of MCC being independent of the particle preparation technique. However, it is suggested that differences in moisture content observed may be due to differences in the shape and size of pores which are opened by the penetrating water molecules, resulting in a relatively high proportion of larger pores in which water may condense. This proposal is however speculative. The results of the present study also suggest that the increased compactibility observed by Millili & Schwartz (1990) on granulating MCC with alcohol instead of water may have been due to reduced intragranular collapse and thus bonding. Because of the likely presence of residual solvents in

the granules together with economical and ecological disadvantages associated with solvent exchange drying, WAN- and WA-drying of granules containing MCC is considered to be in general commercially unfavourable despite potential benefits in terms of compactibility. However, on a more fundamental scientific level the present results appear to support the theory that quasi-hornification is responsible for the reduction in compactibility of MCC observed following wet granulation. Results of the present investigation also suggest that granule compactibility may not be entirely related to enhancement of specific surface areas but rather to prevention of loss of surface areas.

Chapter 8. A study of the effect of wet granulation on the solubility (cohesion) parameters of MCC

8.1 Introduction and objectives

Solubility (cohesion) parameters provide a means for estimating forces such as dispersive and non-dispersive forces acting at the surface of a solid. Thus, they provide information regarding the availability of different types of adsorption sites. In the case of liquids, solubility parameters provide information regarding their ability to interact with similarly characterised solids or liquids. Although first applied to the characteristation of polymers and organic solvents, the solubility parameter approach has been extended to non-polymeric solids and inorganic liquids. Furthermore, solubility parameters have been found to successfully describe and predict the adhesive energy of various lubricants with compression aids in both binary (Rowe, 1988a), tertiary (Rowe, 1988b), quaternary and quinary (Ahmed, 1989) systems. Phuoc et al (1986 and 1987) were the first to suggest that solubility parameters could provide a means for predicting the ability of drugs to interact with excipients. However, although the solubility parameters for two excipients, MCC and anhydrous lactose were determined by Phuoc et al (1986, 1987), solubility parameters were not reported for drugs and these workers did not test their usefulness for predicting the physical stability of drug - excipient blends. In their studies, Phuoc et al (1986 and 1987) determined the total and partial solubility parameters of lactose monohydrate and ungranulated MCC (Avicel PH-101) using inverse gas chromatography (IGC). IGC is an extension of conventional gas chromatography (GC), the difference being that IGC involves characterisation of the stationary phase as opposed to characterisation of the gaseous phase as in conventional GC.

The aims of this part of the study were to examine the effect of wet granulation on the solubility (cohesion) parameters of MCC obtained using an IGC technique. In section 3.4.1 it was suggested that wet granulation of MCC results in increased hydrogen bonding or quasi-hornification of the excipient. If correct, this theory may be extended by considering that wet granulation may reduce the availability of hydroxyl groups on crystallite MCC surfaces for hydrogen bonding, that is reduce the 'hydrophilicity' of surface forces in comparison with the ungranulated material. Such differences might be quantifiable

using the solubility parameter approach and would further support the theory of quasi-hornification following granulation of MCC.

8.2 Theoretical considerations

Hansen (1969) defined the solubility parameter of a liquid as the square root of its cohesive energy density:

$$\delta_t = \left(\frac{\Delta E_t}{V}\right)^{1/2} = \left(\frac{\Delta H - RT}{V}\right)^{1/2} \qquad \text{Equation 8.1}$$

where δ_t is the total solubility parameter, ΔE_t is the total cohesive energy (energy of evaporation or molar internal energy) of the liquid (usually at 25°C), V is the molar volume of the liquid, ΔH is the molar enthalpy of vapourization, R is the ideal gas constant, and T is the absolute temperature.

E_t may be subdivided into contributions from various types of intramolecular interactions such as dispersion (non-polar) forces (E_d), permanent dipole - permanent dipole forces (E_p), and hydrogen bonding forces (E_h) (Hansen, 1969):

$$E_t = E_d + E_p + E_h \qquad \text{Equation 8.2}$$

It should be noted that the above subdivisions are approximate (Phuoc et al, 1986). Dividing each term in equation 8.2 by the molar volume of the solvent, and substituting the partial cohesive energy densities with partial solubility parameters yields equation 8.3 (Phuoc et al, 1986):

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad \text{Equation 8.3}$$

where δ_d, δ_p, and δ_h, are the dispersion, polar, and hydrogen bonding components of the solubility parameter respectively. Values for δ_d, δ_p, and δ_h have been reported by Hansen (1969) for a number of common polar and non-polar solvents.

Solubility parameters, primarily defined for liquids may, be applied to solids by considering them as supercooled liquids (Barton, 1985). However,

determination of solubility parameters for solids is more difficult than for liquids since the energy of vapourisation of solids cannot readily be determined. Phuoc et al (1986) developed a relationship describing the energy of adsorption of an adsorbate onto an adsorbent during gas - solid chromatography in terms of the partial solubility parameters of the adsorbate and solid:

$$-\Delta E^A = V_i(\delta_d^i \delta_d^j + \delta_p^i \delta_p^j + \delta_h^i \delta_h^j) \qquad \text{Equation 8.4}$$

where ΔE^A is the energy of adsorption of an adsorbate i onto the surface of an adsorbent solid j, and V_i is the molar volume of the adsorbate. It should be noted that although commonly termed solubility parameters, the solid in question does not have to possess good solubility in the probes used, or indeed in any commonly employed solvents since the parameters refer to the ability of the solid to interact with other substances rather than solely its ability to dissolve in the substance.

Using the relationship defined in equation 8.4, Phuoc et al (1986) have developed a chromatographic method for determining the solubility parameters of solids which involves:

1) Packing of the solid to be characterised, which must not be volatile, into a GC column. The retention times and from this the retention volumes of a series of molecular probes with known solubility parameters and molar volumes are then determined at a series of column temperatures using an inert carrier gas.

Band migration in chromatography is determined by the equilibrium distribution of the solvent between the stationary and moving phases. The IGC technique involves introduction of the probes by "null injection" (less than 1 μl[3]). In this case the chromatographic peaks should be symmetrical. Under these conditions the specific retention volume can be considered equivalent to the partition coefficient (Atkinson & Curthoys, 1978). The specific retention volume of a molecular probe is the amount of carrier gas required to elute the probe from a column containing 1 gram of interacting stationary phase material and may be calculated as described below. The solvents are chosen so as to adequately represent the range of possible forces of interaction between the solvents and stationary phase without causing excessive experimental work. Retention times must be corrected to account for the dead time of the column under the conditions employed. The dead time is derived from the retention times of a series of alkanes from the relationship in equation 8.5 using multilinear regression.

$$t_r = e^{(an+b)} + t_m \qquad \text{Equation 8.5}$$

where t_r is the experimentally determined retention time of each solvent under similar chromatographic conditions, n is the number of carbon atoms in the alkane, t_m is the dead time for the column under those conditions, and a and b are constants. The corrected retention time, t_r' of the probes can then be determined from:

$$t_r' = t_r - t_m \qquad \text{Equation 8.6}$$

The retention volume is given by the corrected retention time multiplied by the flow rate of the carrier gas through the column (Atkinson & Curthoys, 1978). The apparent flow rate of the carrier gas can be measured using a soap bubble flowmeter. The actual flow rate through the column is determined by applying corrections to the measured flow rate which account for the temperature of the column, the pressure drop across the column, and the pressure drop across the soap bubble flow meter. The specific retention volume, $V_g'_{(Tc)}$, is obtained by dividing the retention volume by the mass of stationary phase in the column. The complete expression for the determination of $V_g'_{(Tc)}$ for each solvent at each temperature thus becomes (Atkinson & Curthoys, 1978):

$$V_g'_{(Tc)} = t_r' \cdot \frac{D'}{M^s} \cdot \frac{T_c}{T_{amb}} \cdot \frac{3}{2} \cdot \frac{(P_i/P_o)^2 - 1}{(P_i/P_o)^3 - 1} \cdot \frac{P_o}{P_{atm}} \qquad \text{Equation 8.7}$$

where D' is the apparent flow rate measured by a soap bubble flow meter at ambient temperature, T_c is the temperature of the column, T_{amb} is the temperature of the flow meter, P_i is the pressure at the column entrance, P_o is the pressure at the exit of the column, M^s is the total mass of the stationary phase.

2) Calculation of the energy of adsorption of each probe on the solid stationary phase.

The energy of adsorption, ΔE^A, is related to the specific volume of retention, $V_g'_{(Tc)}$, determined at the temperature of the column, T_c using equation 8.8 below: (Atkinson & Curthoys, 1978):

$$\ln V_{g\,(Tc)}^{\prime} = - \frac{E^A}{RT_c} + \text{constant} \qquad \text{Equation 8.8}$$

Thus, a plot of the natural logarithm of the specific retention volume against the reciprocal of the absolute temperature of the column (sometimes referred to as a retention diagram) allows the differential change in internal energy to be determined for each probe.

3) Calculation of the partial parameters of solubility of the solid phase from knowledge of the molar volumes, partial solubility parameters, and the energies of adsorption of the selected probes by multilinear regression in accordance with equation 8.4 above.

8.3 Method

The stationary phases characterised were 75-90 μm sieve fractions of ungranulated and wet granulated MCC (Emcocel 50M, BN 8259, Edward Mendell, Patterson, New York, U.S.A.). The granules were prepared according to the method described in section 3.2.1 using 150 g MCC and 105 g distilled water which corresponded to 41.2 $\%^{w}/_{w}$ water in the wet mass, and dried using the method described in section 3.2.2. The appropriate sieve fractions of ungranulated and granulated MCC were obtained using the method described in section 2.2.1. Both ungranulated and granulated MCC materials were dried over silica gel for one week prior to testing. Glass chromatographic columns, 1 meter in length and having an internal diameter of approximately 2 mm, were used. Column packing was achieved using mechanical vibration and by applying pressure using compressed air. Glass wool was used to plug each end of the tube. The weight of the material introduced into the column was recorded. Glass columns were used in preference to copper columns since by using a transparent column it was possible to ensure that the column had been filled reasonably uniformly without the introduction of large voids. This was particularly important in the case of ungranulated MCC because of its poor flow characteristics. This advantage of glass columns was considered to outweigh the disadvantage associated with their fragility which limits the amount of vibration which can be used to fill the column and therefore may result in a loosely packed column.

The gas chromatograph (Type F33, Perkin Elmer, London, U.K.) used was equipped with a flame ionisation detector. Columns were outgassed at 85°C for 24

hours in a current of nitrogen before performing measurements. Nitrogen was also employed as the carrier gas for retention time determinations. The molecular probes employed were: n-pentane, n-hexane, n-heptane, n-octane, n-nonane, n-decane, acetonitrile, methanol, ethanol, propan-1-ol, and carbon tetrachloride. All solvents were of analytical H.P.L.C. grade, and were used without further treatment. The probes used in the present study included those found by Phuoc et al (1987) to provide accurate and precise results for determining the solubility parameters of Avicel PH-101 using a minimal number of solvents, except that in the present study benzene was not used because of its relatively high toxicity. The injection volume for each solvent was 1 μl^3 or less. The injection and detection temperature was 100°C. Retention times for each probe were measured in triplicate at a series of column temperatures between 39 and 95°C, and the mean retention times (t_r) calculated. Temperature consistency is critical to the accuracy of the determinations and for this reason, although the equipment did not allow the temperature to be varied in stages less than 5°C, the temperature was monitored using a thermocouple placed around the column approximately at its midpoint connected to a digital meter. At each preset temperature the temperature was found to remain reasonably stable (mean ± 0.1°C), although in some cases it varied considerably from the nominal temperature set on the chromatograph. The thermocouple reading was used in preference to the preset temperature reading in all calculations. Retention times were recorded using an integrator (Type 3390 A, Hewlett Packard Ltd., Bracknell, Berks., U.K.). The apparent gas flow rate at each temperature was measured at each column temperature using a soap bubble meter and was assumed not to alter during or between measurements at a given temperature. Inlet pressure was recorded using the inlet pressure gauge on the chromatograph. Outlet pressures during flow meter measurements were taken to equal atmospheric pressure. Atmospheric pressure and temperature were recorded using a mercury barometer and a mercury thermometer respectively.

8.4 Calculations, results and discussion

The uncorrected retention times of the probes on ungranulated and granulated Emcocel, together with the experimental conditions under which they were determined are presented in tables ii.1 and ii.3 respectively (appendix ii). The dead time for the column at each temperature was determined from the retention times of the alkanes according to equation 8.5 by multilinear regression using an iterative technique which calculated t_m, a and b simultaneously (Minsq software program, Micromath Inc. New York, U.S.A.). Dead times are presented

in tables ii.1 and ii.3 (appendix ii). Corrected retention times for the probes on ungranulated and granulated MCC respectively calculated from equation 8.6 are presented in tables ii.2. and ii.4 respectively. The molar volumes, partial and total solubility parameters of the probes taken from Phuoc et al (1986 and 1987) are listed in table 8.1.

The specific retention volumes for each probe at each temperature were determined according to equation 8.7, and are presented in tables ii.2 and ii.4 for ungranulated and granulated MCC respectively. Using linear regression, the gradient and correlation coefficient of the plot of ln $V'_{r(Tc)}$ against $1/T_c$ was determined. The adsorption energy for each probe was calculated from the gradient of the retention diagrams in accordance with equation 8.8. It was found that for some probes the retention diagrams exhibited poor correlation coefficients. Specifically pentane, hexane, heptane, acetonitrile, ethanol, methanol and carbon tetrachloride yielded particularly poor correlation coefficients (less than 0.99 for both ungranulated and granulated MCC). Of the probes they employed, Phuoc et al (1987) found that the adsorption energies of methanol and acetonitrile on Avicel were poorly reproducible, and they suggested that this may have been caused by the short retention times of these two probes (Phuoc et al, 1986). Phuoc et al (1986) found that the solvents which yielded adsorption energies which gave acceptably precise and accurate solubility parameters with the minimum amount of experimental work for Avicel were decane, carbon tetrachloride, benzene, acetonitrile, methanol, and ethanol. The probes used in the present study to evaluate the partial solubility parameters for the two samples of MCC in the present study, together with their adsorption energies are listed in table 8.2. These were chosen empirically by consideration of the correlation coefficients of the retention diagrams and the solubility parameters of the probes. Use of a narrow range of solvents with similar parameters was avoided.

The adsorption energies, molar volumes and partial solubility parameters of the selected solvents were used to calculate the partial solubility parameters of ungranulated and granulated MCC respectively according to equation 8.4 by multilinear regression, again using an iterative technique. Further, using the relationship in equation 8.3, the total solubility parameter for ungranulated and granulated MCC was evaluated. The solubility parameters are listed in table 8.3. Also in table 8.3 the solubility parameters for another commercial form of ungranulated Avicel PH-101 as determined by Phuoc et al (1987) are given.

Table 8.1. Molar volumes, partial and total solubility parameters of the solvents used in the present study (taken from Phuoc et al, 1987, and adjusted to S.I. derived units)

Solvent	Molar volume m^3mol^{-1} x10^{-4}	Solubility parameters $MPa^{1/2}$ δ_d	δ_p	δ_h	δ_t
n-pentane	1.162	14.36	0.0	0.0	14.36
n-hexane	1.316	14.81	0.0	0.0	14.81
n-heptane	1.474	15.18	0.0	0.0	15.18
n-octane	1.640	15.44	0.0	0.0	15.44
n-nonane	1.800	15.65	0.0	0.0	15.65
n-decane	1.959	15.79	0.0	0.0	15.79
acetonitrile	0.526	15.34	18.00	6.14	24.34
methanol	0.410	15.18	12.27	22.30	29.21
ethanol	0.590	15.81	8.80	19.43	26.43
propan-1-ol	0.750	15.85	6.75	17.39	24.48
carbon tetrachloride	0.960	17.69	0.0	0.0	17.69

Table 8.2. Adsorption energies of selected probes on ungranulated and wet granulated MCC obtained by gas solid chromatography (95% confidence limits given in parentheses)

Solvent	Adsorption energy on ungranulated MCC ($kJ\ mol^{-1}$)	Adsorption energy on wet granulated MCC ($kJ\ mol^{-1}$)
n-octane	36.6 (±4.4)	32.6 (±4.5)
n-nonane	45.6 (±6.8)	38.8 (±3.3)
n-decane	44.5 (±4.3)	41.4 (±3.5)
acetonitrile	24.2 (±4.5)	24.8 (±4.0)
ethanol	38.5 (±6.8)	39.1 (±11.2)
propan-1-ol	42.1 (±3.9)	40.1 (±3.3)

Table 8.3. Partial and total solubility parameters for ungranulated and wet granulated Emcocel, and for ungranulated Avicel (standard deviations are given in parentheses).

Material	Solubility parameters $MPa^{1/2}$			
	δ_d	δ_p	δ_h	δ_t
Ungranulated MCC (present study)	15 (0.5)	7 (3)	17 (2)	24
Wet granulated MCC (present study)	13 (0.7)	10 (4)	16 (3)	23
Ungranulated MCC (Phuoc et al, 1987)	18.82 (1.02)	13.71 (2.05)	32.33 (1.43)	39.84

From table 8.3 it can be seen that although the absolute values differ, the solubility parameters obtained in the present study for Emcocel follow a similar rank order to those evaluated by Phuoc et al (1987) for Avicel. Differences between data obtained in the present study for ungranulated MCC and data obtained by Phuoc et al (1987) could arise from differences between the commercial forms of MCC and/or from differences between the instrumentation and experimental techniques used.

The solubility parameters of ungranulated and granulated MCC were found to have similar rank order to each other, that is the hydrogen bonding term was greater than the dispersion term which was greater than the polar term (table 8.3). This indicates that the surface of both ungranulated and granulated forms of MCC excipient have high affinities for hydrogen bonding. The dispersion component for ungranulated Emcocel was however found to be greater than for granulated Emcocel (table 8.3). Using the t-test the dispersion component of the solubility parameters for the two samples were found to be significantly different at a level of 1%. However the polar and hydrogen bonding terms and the total solubility parameter were not found to be significantly different between the two materials. The slightly reduced dispersive component for granulated MCC suggests that granulation resulted in a small increase in the ability of the excipient to undergo polar and/or hydrogen bonding with adsorbates which, in turn, suggests an increase in the number of available hydroxyl groups following wet granulation.

This tends to contradict the theory of quasi-hornification proposed in section 3.4.1 to explain the physico-mechanical behaviour of wet granulated MCC. However, it has been noted elsewhere that solubility parameters cannot be expected to predict relatively minor differences in the behaviour of materials (Barton, 1985). In addition, there are limitations to their precise determination due to the cumulative nature of inaccuracies involved in the stages of adsorption energy determinations. Thus, good experimental technique is crucial if meaningful and absolute results are to be obtained (Bolvari et al, 1989).

Sources of possible error in the above method include errors in determination of and fluctuations in the flow-rate and the column temperature. In addition, since the retention times were generally short, increasing the retention time for example by using a longer column or by increasing the packing density of the stationary phase may reduce errors involved in retention time determination. Furthermore, the carrier gas and the probes were not of very high purity, and the injection volume, although small, could have been reduced further by using the procedure proposed by Bolvari et al (1989) thereby reducing errors associated with the dependence of retention time on injection volume. In addition, the use of a wider range of probes, in particular the use of a greater number of probes capable of hydrogen and polar bonding may improve the accuracy of the parameters obtained.

Although the dispersion terms for ungranulated MCC was approximately 16 % greater than for granulated MCC, which was statistically significant, consideration of the errors involved in and the limitations of the experimental technique it is suggested that this difference has limited significance in physico-chemical terms. However, the absence of large differences between the solubility parameters of ungranulated and granulated MCC suggests that granulation does not reduce MCC compactibility by altering the surface and therfore bonding chacteristics of MCC. The above results may be interpreted as being broadly consistent with the theory of quasi-hornification; that granulation reduces MCC compactibility by altering the inherant deformation characteristics of MCC. By improving the experimental technique as discussed above it may be possible in future to evaluate differences between the two cellulosic materials with a greater degree of certainty.

Chapter 9. Moisture sorption of ungranulated and granulated MCC

9.1 Objectives

The main aim of this part of the present study was to investigate the effect of wet granulation on the moisture sorbing capability of MCC. Additionally, the effects of severe pre-drying of ungranulated MCC on sorption hysteresis, and the influence of commercial source on moisture adsorption and desorption isotherms were investigated.

9.2 Materials and Methods

Ungranulated MCC from two commercial sources was used; Emcocel 50M (lot 8259, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) and Avicel PH-101 (lot 6547, FMC Corp., Philadelphia, U.S.A.). Granules were prepared using 150 g Emcocel with 105 g distilled water which corresponded to a weight of 41.2 % water in the final weight of wet mass, according to the general method described in section 3.2.1. Following wet screening granules were dried using the method described in section 3.2.2. Ungranulated and granulated MCC were size separated according to their sieve diameter using the method described in section 2.2.1. In the following study, particles in the sieve diameter range 75-90 μm were used.

Moisture adsorption by samples of MCC was determined by a gravimetric method. All weighings were performed using an analytical balance (Sauter RE1614, August Sauter, Albstadt-Ebingin, Switzerland) having a precision of ± 0.1 mg. In order to improve the accuracy and speed with which samples could be weighed, the balance was placed on a vibration-damped table. Ten 500 ± 1 mg samples of each of the three MCC types were weighed into specially designed tared glass tubes 18 mm in diameter and 15 mm in height. Five samples of each MCC type were dried under reduced pressure at elevated temperatures. This was achieved by firstly storing the samples overnight in desiccators containing silica gel, followed by drying in a vacuum oven containing silica gel at an estimated pressure of 13 Nm^{-2} and at 70°C. During the first 4 hours of drying a vacuum was continuously applied after which the outlet to the vacuum pump was closed and the samples retained in the heated oven under vacuum for a further 20 hours after

which the heater was switched off. The aforementioned drying technique did not visibly cause charring of the samples and was similar to that employed by Hollenbeck et al (1978) to dry samples of Avicel PH-101: They reported that the moisture content of MCC samples after drying under these conditions was only approximately 0.2 $\%^{w}/_{w}$ less than obtained following additional drying at 100°C and ambient pressure (Hollenbeck et al, 1978). Thus, it was considered that the drying technique was severe. When the evacuated drying chamber had reached room temperature, air which had been dried over silica gel was admitted into the chamber slowly so as to avoid fluidising the samples. The samples were removed from the oven and quickly transferred to a desiccator containing silica gel and transported to the nearby balance on which they were rapidly reweighed. Because of the relatively large number of samples to be weighed from each dessicator in this study, the order of sample weighing was randomised using an approximated latin square. In addition, from the sample weight and the time of exposure to the atmosphere before weighing, a time based correction factor was used to adjust sample weights to approximately compensate for the gain in moisture due to exchange with the atmosphere over the period during which weighings were performed.

Dried samples were stored in a previously equilibrated dessiccator at 25°C containing saturated lithium chloride solution which has been reported to maintain a relative humidity of 11 % at this temperature (Nyqvist, 1983). Samples were considered to have reached their equilibrium moisture content within 21 days although it was recognised that this storage time was likely to be longer than necessary for equilibration since studies for adsorption of water vapour onto Avicel PH-101 reported by Hollenbeck et al (1978) suggested that equilibration at relative humidities up to 100 % was complete after a maximum of five days. After equilibration, samples were reweighed quickly avoiding excessive exchange of moisture with the atmosphere. Again, the sample weights were again approximately corrected for time of exposure to the atmosphere as described above. Samples were similarly equilibrated in turn in desiccators maintained at increasing humidities. The saturated salt solutions used to achieve the desired range of relative humidities are given in table 9.1. The relative humidities in the dessicators achieved by using the selected salt solutions were assumed to be 33 %, 53 %, 75 %, 84 % and 94 % in accordance with the humidities reported by Nyqvist (1983). Since stirred desiccators could not be used due to space

constraints in the constant temperature cabinets, it is recognised that these relative humidities represent only approximate values. At 53 %, 75 %, 84 % and 94 % humidities, the remaining five undried samples of each type were equilibrated in the same desiccators. The order of sample weighings was varied for weight determinations at each relative humidity and weights corrected as described above.

After determining sample weights at 94 % humidity, all samples were stored in desiccators in order of progressively decreasing humidities which were achieved using the saturated solutions given in table 9.1. Following storage at the lowest relative humidity, all samples were severely dried in a vacuum oven using the procedure described above to determine the dry weight of the previously undried samples, and to recheck the dry weight of the previously dried samples, the latter being found to be within ± 0.03 g of the initial sample weight. Moisture contents at each humidity were determined using equation 9.1 where the weight of sample and tube after equilibration minus the weight of the empty sample tubes gave the 'wet weight' of sample. The dry weights of the samples were determined after moisture sorption and desorption and severe drying.

$$\% \text{ moisture content} = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100\ \% \qquad \text{Equation 9.1}$$

Table 9.1. Relative humidities achievable using saturated salt solutions at 25°C (selected from Nyqvist, 1983)

Salt	Relative humidity (%)
Lithium Chloride	11.3
Magnesium Chloride	32.8
Magnesium Nitrate	52.8
Sodium Chloride	75.3
Potassium Chloride	84.3
Potassium Nitrate	93.7

9.3 Results

Changes in moisture content which occurred during adsorption and desorption cycles for MCC stored in different relative humidities are given in tables 9.2 and 9.3 respectively. The moisture adsorption and desorption profiles for the samples are shown in figures 9.1 and 9.2. In accordance with the categories suggested by Brunauer et al (1940), the isotherms are consistent with those described as Type II, which generally occur during gas adsorption onto non-porous surfaces or onto microporous surfaces which allow multimolecular adsorption to occur.

9.4 Discussion

9.4.1 Effect of wet granulation on the moisture sorbing properties of MCC

In Chapters 3, 4, 5, and 7 above, it was reported that wet granulation of MCC using similar experimental conditions to those used in the present Chapter resulted in an appreciable reduction in the compactibility of Emcocel. A theory developed in section 3.4.1 suggested that the reduction in granule compactibility caused by wet granulation arose from collapse of particle structures during drying of wet MCC granules which resulted in increased intraparticle bonding. The phenomenon was termed quasi-hornification (section 3.4.1) since it was considered to be similar to the phenomenon of hornification of cellulose fibres which has been described elsewhere in the context of pulp and paper making (section 1.4.2).

As discussed in section 1.4, studies by other workers on the strength of paper prepared from pre-dried and never-dried cellulose fibres provide indirect evidence that hornification results in increased interfibre bonding which is irreversible on rewetting. This conclusion is based on the findings that i) the strength of paper prepared from never-dried fibres is significantly greater than that the strength of paper prepared from dried and reslushed fibres (section 1.4.2) and ii) dried fibres exhibit lower 'water retention values' in comparison with undried fibres (section 1.4.4). As discussed in section 1.3.1.5, it has been suggested that the physical state of the water molecules may affect the degree of interaction of cellulose with water (Jeffries et al, 1968). However, it would be expected that an irreversible reduction in the accessibility of cellulose fibres to liquid water as a result of hornification may be accompanied by an irreversible reduction in the

Table 9.2. Isothermal adsorption data for water sorbed onto ungranulated Emcocel, wet granulated Emcocel, and ungranulated Avicel at 25°C (mean values, with 95 % confidence limits given in parentheses)

Relative Humidity (%)	Moisture Content ($\%^{w}/_{w}$)					
	Ungranulated Emcocel		Ungranulated Avicel		Granulated Emcocel	
	predried	undried	predried	undried	predried	undried
11.3	1.98 (0.02)	- - -	1.96 (0.02)	- - -	2.02 (0.02)	- - -
32.8	3.95 (0.01)	- - -	3.97 (0.02)	- - -	4.08 (0.01)	- - -
52.8	5.71 (0.02)	5.98 (0.05)	5.64 (0.02)	6.02 (0.04)	5.86 (0.01)	6.02 (0.03)
75.3	8.75 (0.05)	9.11 (0.01)	8.62 (0.04)	8.93 (0.03)	8.88 (0.02)	9.32 (0.01)
84.3	10.75 (0.03)	10.98 (0.02)	10.79 (0.02)	10.90 (0.03)	10.97 (0.02)	11.24 (0.03)
93.7	14.38 (0.07)	15.20 (0.06)	14.26 (0.05)	14.88 (0.06)	14.45 (0.04)	15.30 (0.03)

Table 9.3. Isothermal desorption data of ungranulated Emcocel, wet granulated Emcocel, and ungranulated Avicel at 25°C (mean values, with 95 % confidence limits given in parentheses)

Relative Humidity (%)	Moisture Content ($\%^{w}/_{w}$)					
	Ungranulated Emcocel		Ungranulated Avicel		Granulated Emcocel	
	predried	undried	predried	undried	predried	undried
84.3	12.23 (0.06)	12.98 (0.03)	12.28 (0.06)	12.86 (0.06)	12.48 (0.02)	13.13 (0.02)
75.3	10.26 (0.02)	10.58 (0.03)	10.34 (0.01)	10.54 (0.03)	10.52 (0.02)	10.87 (0.02)
52.8	6.88 (0.03)	7.01 (0.02)	6.94 (0.01)	6.95 (0.04)	7.10 (0.02)	7.21 (0.01)
32.8	4.66 (0.03)	4.82 (0.04)	4.70 (0.02)	4.83 (0.02)	4.81 (0.02)	5.00 (0.01)
11.3	2.51 (0.02)	2.62 (0.01)	2.56 (0.02)	2.63 (0.02)	2.60 (0.01)	2.71 (0.02)

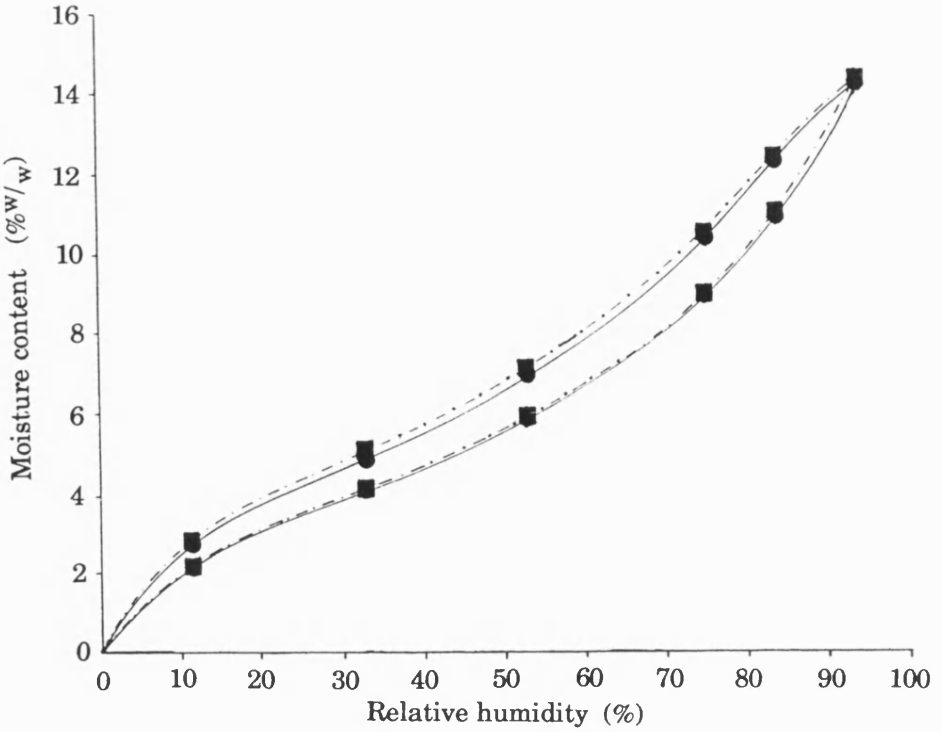


Figure 9.1 Moisture adsorption - desorption isotherms for; i) pre-dried ungranulated Emcocel; —●—● and ii) pre-dried granulated Emcocel;-■- -■-- (Note: 95% confidence limits are within the data points).

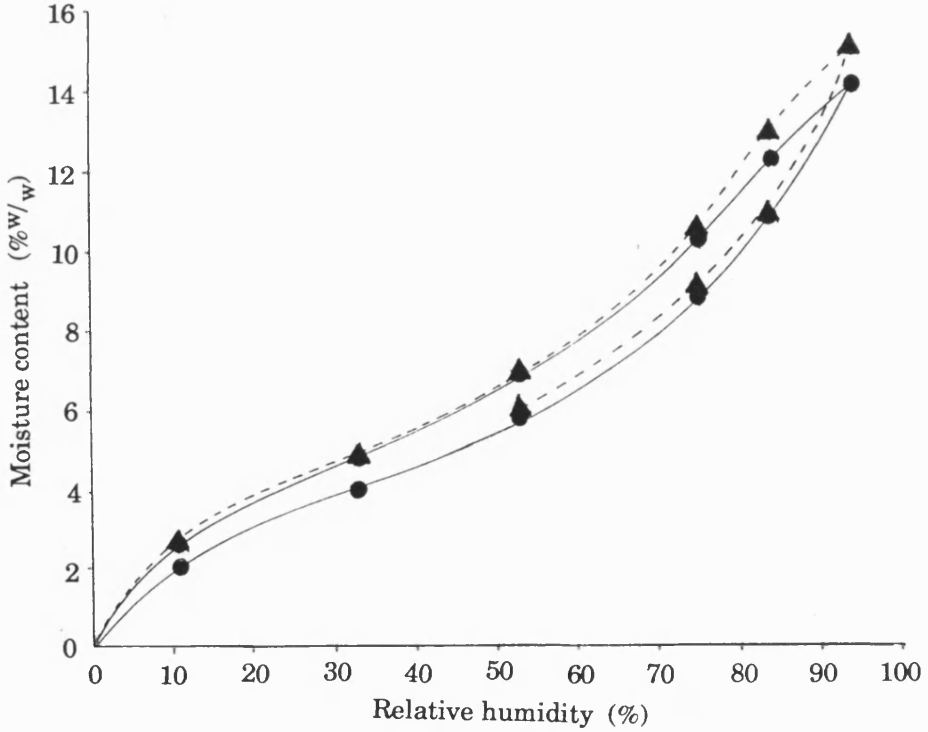


Figure 9.2 Moisture adsorption - desorption isotherms for; i) pre-dried ungranulated Emcocel; —●—● and ii) un-dried ungranulated Emcocel; - ▲- -▲- - (Note: 95% confidence limits are within the data points).

ability of the fibres to adsorb water vapour. Such a study does not appear to have been reported directly in the literature. Further, if the theory that wet granulation caused hornification held true for MCC, granulation may be expected to reduce the ability of MCC to adsorb water vapour. If this situation existed it would have important theoretical and practical significance since it would wholly or at least partially account for the reduction in compactibility of MCC observed following wet granulation. As discussed in section 1.5.4.5, this is because a reduction in the amount of adsorbed moisture would be expected to reduce the compactibility of MCC.

Results of the present investigation do not, however, indicate that wet granulation reduces the ability of MCC to adsorb water vapour. The magnitude of any difference between the moisture contents for ungranulated and wet granulated MCC differed with the relative humidity (tables 9.2 and 9.3). At some relative humidities there was no significant difference. However, at other relative humidities granulation did significantly affect the moisture content. If there was any difference, it was found that wet granulation resulted in a marginal increase in the moisture sorbing ability of Emcocel. The latter occurred irrespective of whether the samples were severely pre-dried (tables 9.2 and 9.3 and figure 9.1) or not pre-dried (tables 9.2 and 9.3). Thus, the decrease in specific surface area as determined by nitrogen adsorption following wet granulation of MCC using the present level of granulating water (section 3.3.1) did not appear to reduce the accessibility of MCC to water vapour adsorption. Further, and importantly, wet granulation does not appear to reduce MCC compactibility by reducing the moisture content.

A possible interpretation of the above results is that unlike cellulose fibres in contact with liquid water, the quasi-hornification of MCC is reversible on contact with water vapour. There are important physical and chemical differences between native cellulose and MCC. The cellulose chain length in MCC is lower than in holocellulose and furthermore the degree of crystallinity of MCC is greater than for holocellulose (section 1.5.2). These two factors may contribute to a lower degree of lateral bonding as a result of the quasi-hornification process in MCC; in the case of MCC the cellulose units (crystallites) may be less conformable when wet in comparison with microfibrils of cellulose fibres. This, combined with their smaller size and random packing, may result in the original particles of ungranulated MCC exhibiting incomplete intracrystallite bonding upon drying.

Areas of low intracrystallite bonding may be able to adsorb moisture, the adsorbed moisture perhaps able to disrupt the intermolecular hydrogen bonding within the newly bonded intercrystallite regions. If the theory of 'reversible hornification' developed above is correct, water vapour adsorption would be expected to result in increased disruption of intermolecular hydrogen bonds within granulated MCC in comparison with ungranulated MCC. There is some indirect evidence for such behaviour and this is discussed further in Chapter 10 below. However, if the proposed intraparticle bonding of MCC arising from wet granulation is completely reversed on adsorption of water vapour, it might be expected that under ambient humidity, adsorbing water molecules would plasticise the granules and restore particle compactibility to pre-granulation levels.

As discussed in other Chapters in the present study, under ambient conditions MCC granules exhibit reduced compactibility in comparison with ungranulated MCC. The mechanism by which granulation reduces MCC compactibility is consistent with the theory of increased intraparticulate bonding. A reduction in compactibility following granulation and retention of intraparticulate bonding under ambient conditions suggests that reversal of hornification arising from water vapour adsorption is incomplete. Since the moisture absorbing ability of MCC is not reduced as a result of granulation, it is suggested here that granulation may have altered the granule pore size distribution, and that this may have resulted in granules adsorbing a greater proportion of moisture by condensation in comparison with ungranulated MCC. This effect would offset the reduction in available primary cellulose adsorbtion sites resulting from granulation. Further, results of the present study suggest that with respect to water vapour adsorbtion by granulated MCC, the latter effect, combined with partial reversal of intragranular bonding on water vapour adsorption as discussed in Chapter 10, results in similar moisture absorbtion abilites of ungranualted and granulated MCC.

The reasons for the small increase in the moisture sorbing ability of MCC as a result of wet granulation are unclear. However, it is considered that an increase in the proportion of water condensed in granule pores may more than offset any reduction in primary cellulose adsorption sites resulting in higher equilibrium moisture contents.

9.4.2 Effect of granulation and severe drying on moisture hysteresis in water vapour adsorption - desorption isotherms

Pre-drying of ungranulated Emcocel resulted in a slight reduction in the moisture content over most of the adsorption and desorption isotherms (tables 9.2 and 9.3 and figure 9.2). A similar effect was observed for Avicel and granulated Emcocel (tables 9.2 and 9.3). This suggests that severe drying of MCC caused a marginal reduction in the accessibility of MCC to moisture, which was possibly due to increased intermicrocystal bonding or an increase in the degree of bonding within amorphous regions which was irreversible on equilibration with water vapour. The irreversibility of the bonding may be due to lateral ordering and bonding.

The moisture adsorption-desorption isotherms for ungranulated Avicel have been reported by several workers. Although discrepancies in the absolute values for moisture content at different humidities reported in different studies may be expected due to interbatch variations and variations in the experimental techniques used by different workers, more significantly, the magnitude of the hysteresis effect also varies between studies. For example, in the studies reported by Hollenbeck et al (1978) and Nyqvist (1983), negligible hysteresis was observed at relative humidities up to and including 60 %, with a slightly greater hysteresis reported at higher humidities. In contrast, Bangudu & Pilpel (1985) and Khan & Pilpel (1986) reported greater hysteresis in adsorption-desorption isotherms; at a relative humidity of 60 %, moisture remaining following desorption was approximately 2 $\%^{w}/_{w}$ greater than observed as a result of adsorption. In the studies by Hollenbeck et al (1978) and Nyqvist (1983), it was stated that all samples were predried under reduced pressure at 70°C before determining the isotherms, including the desorption isotherm. However, samples did not appear to have been pre-dried in the studies reported by Bangudu & Pilpel (1985) and Khan & Pilpel (1986) before equilibration at a high humidity and determination of desorption isotherms. In the present study, the magnitude of the adsorption - desorption hysteresis was not found to be substantially altered by severe pre-drying of the samples. This suggests that differences between the adsorption - desorption hysteresis reported by different workers may not be explained by the degree of pre-drying used.

It should be noted that the moisture sorption and desorption isotherms for

ungranulated Emcocel and Avicel were broadly similar for both pre-dried and undried MCC (tables 9.2 and 9.3). This suggests that differences between the compactibilities of Emcocel 50M and Avicel PH-101 reported by other workers are not attributable to differences in the accessibility of the hydroxyl groups on MCC molecules to atmospheric moisture.

Chapter 10. A study of the effect of wet granulation on the heat of adsorption and adsorption kinetics of water vapour by MCC

10.1 Introduction

Although not shown directly, the preceding investigations in the present study have suggested that wet granulation results in increased intraparticulate bonding, perhaps by a phenomenon similar to that termed hornification as discussed in section 3.4.1. However, for MCC used in the present study, any such increased bonding did not appear to reduce the ability of MCC to adsorb water vapour. It was thus proposed that wet granulation of MCC caused a separate, although linked, phenomenon termed quasi-hornification (section 9.4.1). The objectives of the present investigation were to examine the heat evolved and the kinetics associated with heat evolution and vapour pressure decrease during the adsorption of successive doses of water vapour by ungranulated and granulated MCC to examine further the effect of wet granulation on the physical characteristics of MCC and to test the theory of quasi-hornification proposed in sections 3.4.1 et seq..

10.2 Materials and Methods

Ungranulated and granulated MCC powders (Emcocel 50M, lot number 8261, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) were used in the following study. Granules were prepared using 150 g Emcocel with 105 g distilled water, which corresponded to 41.2 % $^{w}/_{w}$ water in the final wet mass, using the general method described in section 3.2.1. Granules were dried following wet screening using the method described in section 3.2.2. Ungranulated and granulated MCC were separated according to their sieve diameters using the method described in section 2.2.1. In the following study, particles in the sieve size range 75 - 90 μm were used which had been stored for 7 days over dried silica gel.

Heats of water vapour adsorption were determined using a Tian-Calvet microcalorimeter (model: MS70, Setram, France) connected to a volumetric apparatus shown schematically in figure 10.1. Prior to installation in the calorimeter, a known weight of each sample was outgassed for 24 hours in a calorimeter cell at 70°C using a diffusion pump. Comparison with results obtained

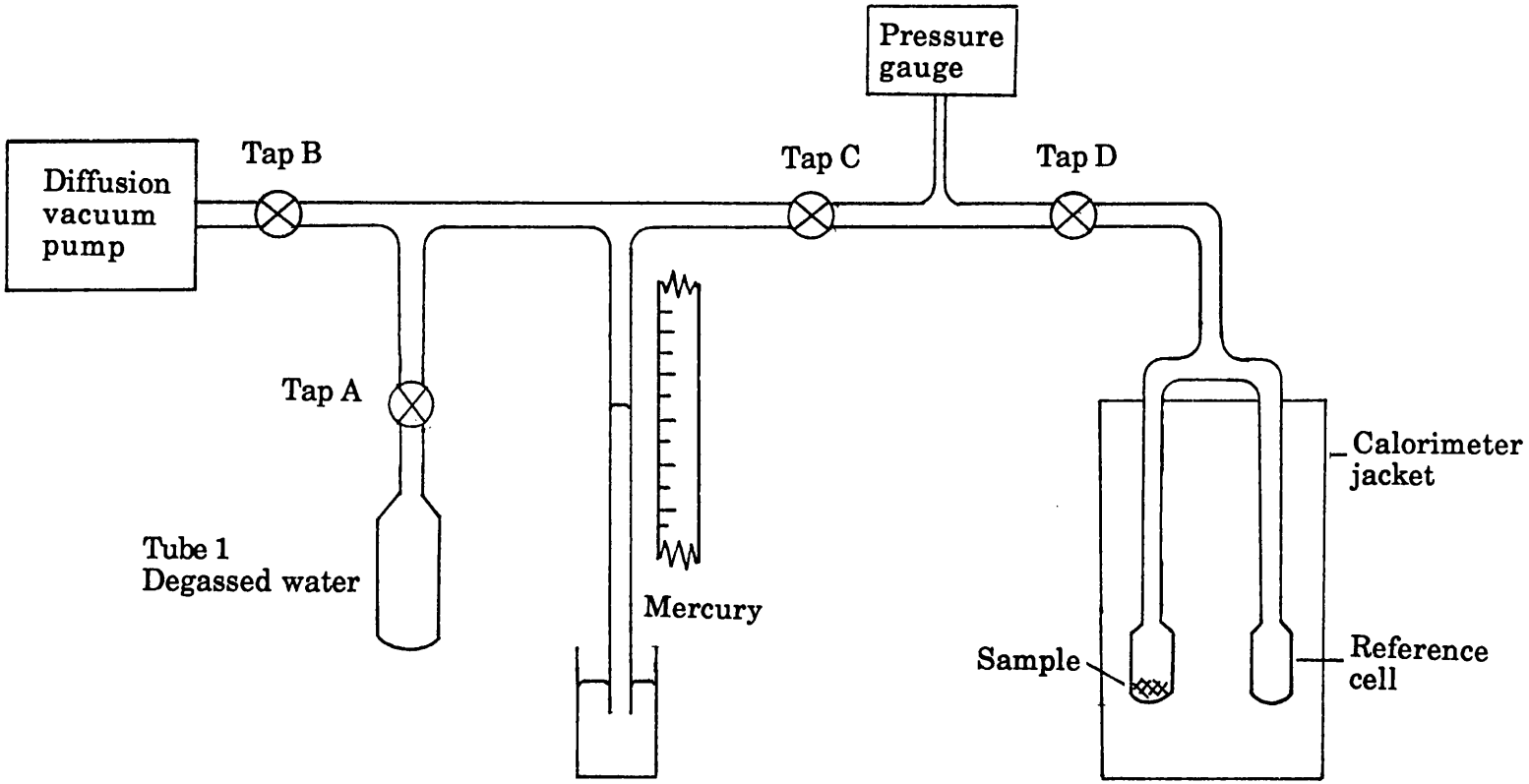


Figure 10.1 Schematic diagram of the microcalorimeter used for water adsorption studies

by Hollenbeck et al (1978) and Zografi et al (1984) for Avicel PH-101 suggested that the degassing procedure used in the present investigation removed much of the bound adsorbed water. The cell was isolated and allowed to cool to ambient temperature before transferring to the calorimeter. The calorimeter cells were maintained at 30.0°C. Room temperature, and thus the temperature of the volumetric apparatus, was maintained at 22.5°C.

The sample was equilibrated with successive additions of water vapour, termed doses, up to a relative water vapour pressure of approximately 15 %. The source of the water vapour was double distilled water prepared gas free by successive freeze-pump-thaw cycles. With taps A and D closed and taps B and C open, the tube space between taps A and D was evacuated for between 10 and 15 minutes (figure 10.1). Following evacuation, taps B and C were closed and a small dose of water vapour from the head space above the water in tube 1 (figure 10.1) was admitted into the tube space between taps B and C by briefly opening tap A manually. The mercury manometer (figure 10.1) provided an estimate of the amount of water vapour admitted. After zeroing the pressure gauge connected to the evacuated tube space between taps C and D, tap C was opened and shortly afterwards closed, admitting water vapour into the tube volume between taps C and D. The pressure exerted by the vapour in the volume between taps C and D was monitored using the pressure gauge. When maximum pressure was attained, tap D was opened fully, allowing water vapour into the sample and reference tubes of the calorimeter. The change in pressure and evolution of heat with time as a result of partial adsorption of the admitted water vapour dose by the samples was recorded electronically and data transferred to an associated computer. Heat output and vapour pressure were monitored until thermal equilibrium had been re-established, which occurred approximately 45 minutes after admission of the vapour dose. The final pressure reading, ($P_{final\ (uncorrected)}$), was recorded manually from the pressure gauge. Tap D was then closed, taps B and C opened, and the tube volume between taps A and D evacuated for 10 to 15 minutes. Following evacuation the gauge pressure was recorded again, and if the pressure was not zero, then the value was subtracted from the final pressure reading following equilibration with the preceding dose of water vapour, ($P_{final\ (uncorrected)}$). This procedure was carried out in order to correct the final pressure readings for errors caused by drift in the gauge output over the sample equilibration period, and provided a corrected final pressure reading following the adsorption process, (P_{final}).

The procedure was repeated with successive doses of water vapour. In general, between successive doses the tubespace between taps A and D was evacuated for between 10 and 15 minutes, with the exceptions detailed immediately below. As a consequence of the large number of doses applied to each sample, data for each sample was acquired over three days. In the case of ungranulated MCC, doses 1 to 5 inclusive were applied on the first day, doses 6 to 13 on the second day, and doses 14 to 20 on the third day. In the case of granulated MCC, doses 1 to 5 inclusive were applied on the first day, doses 6 to 12 on the second day, and doses 13 to 19 on the third day. When samples were left overnight between the last measurements of the previous day and the first of the next day, the tubespace between taps A and D was evacuated continuously for approximately 16 hours. In addition, between doses 10 and 11 supplied to ungranulated MCC and between doses 9 and 10 supplied to granulated MCC an evacuation time of 1.5 hours was used. Because of time constraints, replicate investigations were not performed for each sample type, the results representing single determinations only.

The amount of water sorbed by the sample as a result of equilibration with each dose of water vapour was calculated from the maximum pressure of the water vapour in the tubing between taps C and D before admission into the calorimeter cells, known as the dose pressure (P_{dose}), and from the corrected pressure of the water vapour in the tubing space from tap C to and including the calorimeter cells, (P_{final}), after equilibration with the sample, together with the previously determined volumes of the system. The heat evolved as a result of adsorption was computed by integrating the heat evolved (calorimeter signal) with respect to time. Further details regarding calculation of the results together with full experimental data obtained for adsorption of successive doses of water vapour by ungranulated and granulated MCC are provided in appendix iii. The heat change associated with the adsorption process was used to provide information regarding the degree of hydrophobicity or hydrophilicity of the adsorbate according to the extent by which the heat of adsorption was lower or higher than the heat of liquefaction of water (Fubini et al, 1989). Furthermore, the variation of the heat evolved per mole of water adsorbed as a function of water uptake may provide information regarding the heterogeneity of the chemical reactivity of surface sites (Fubini et al, 1989). In addition, from the amount of water adsorbed at each vapour pressure for doses at relative pressures greater than approximately

5 %, the monolayer capacity and the specific surface area of samples was estimated using the B.E.T. relationship (section 1.5.4.6) using a value of 10.8 $Å^2$ (Lowell & Shields, 1984b) for the cross sectional area of an adsorbed water molecule.

10.3 Results and discussion

B.E.T. analysis of water vapour adsorption isotherms obtained for samples of either ungranulated or granulated MCC is discussed below in section 10.3.4 and indicates a monolayer capacity of approximately 0.036 g water / g solid which corresponds to approximately 0.2 moles water / 100 g solid. In the present investigation, the maximum amount of water vapour adsorbed by either ungranulated or granulated MCC samples was approximately 0.14 moles water / 100 g solid. For this reason, it was assumed that the present results describe adsorption of water molecules in the first monolayer. Furthermore, assuming that the water vapour adsorption behaviour of Emcocel 50M is similar to that of Avicel PH-101, results presented by Hollenbeck et al (1978) would suggest that the adsorption behaviour for cases when less than 0.15 mole water / 100 g solid is adsorbed corresponds to each water molecule forming two bonds with anhydroglucose units of cellulose, perhaps according to the model suggested by Khan & Pilpel (1987) in which each adsorbed water molecule links anhydroglucose units on adjacent cellulose chains.

10.3.1 General trends for heat of adsorption

The overall heat of adsorption per mole adsorbed water for successive doses adsorbed by ungranulated and granulated MCC are shown in figures 10.2 and 10.3 respectively. Heat evolution is assumed to arise as a result of the formation of hydrogen bonds between the adsorbate and water molecules.

The heat evolved per mole adsorbed water for successive doses of water corresponding to a total adsorbed volume less than approximately 0.07 - 0.075 mole water / 100g MCC sample (point x in figures 10.2 and 10.3) varied between successive doses suggesting an energetically heterogeneous adsorption surface. Possible reasons for substantially higher heats of adsorption occurring as a result of equilibration of granulated MCC with dose 6 (figure 10.3) and the relatively low heat of adsorption for dose 13 on granulated MCC (figure 10.3) and for doses 6, 11 and 14 on ungranulated MCC (figure 10.2), in comparison with the trends

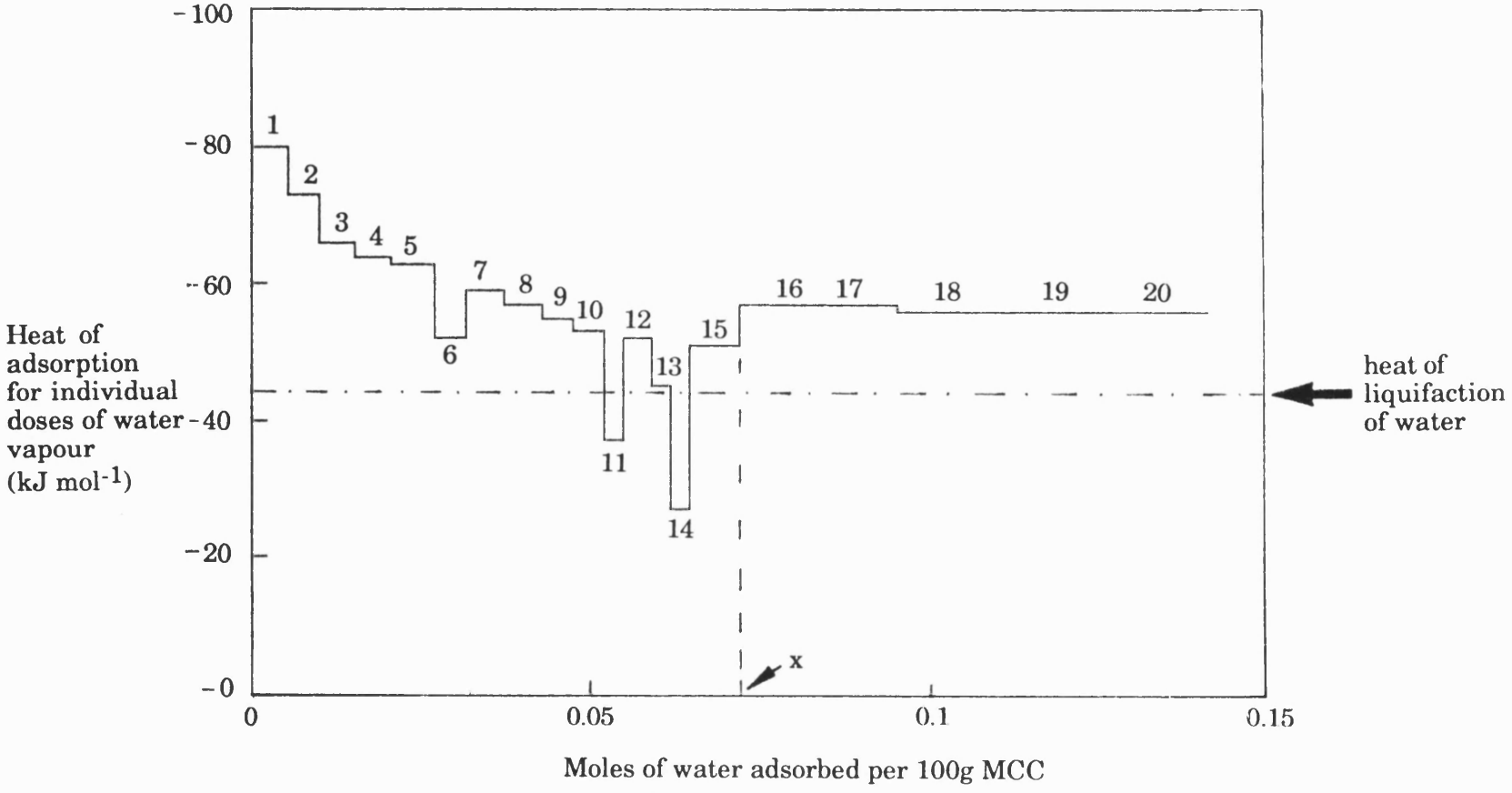


Figure 10.2 The heat of adsorption associated with the uptake of successive doses of water vapour by ungranulated MCC.
Note: The number associated with each bar represents the dose number.

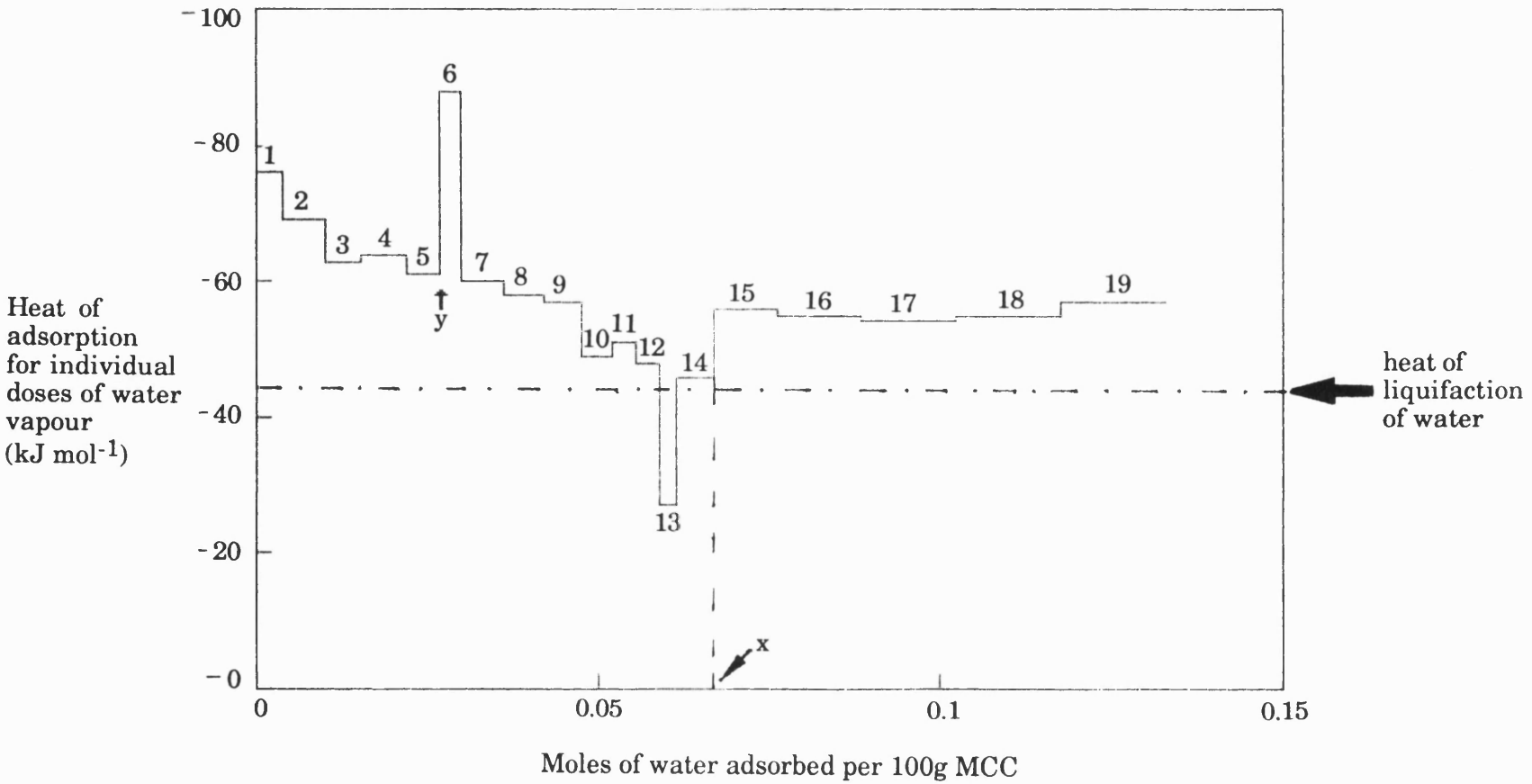


Figure 10.3 The heat of adsorption associated with the uptake of successive doses of water vapour by granulated MCC.
Note: The number associated with each bar represents the dose number.

for the heats of adsorption for other doses are discussed in sections 10.3.2 and 10.3.3 respectively below. However, for both ungranulated and granulated MCC, a trend was found relating changes of heats of adsorption per mole adsorbed water to total water uptake: initially high heats of adsorption were found which then decreased until the total adsorbed water was approximately 0.05 moles water / 100 g solid. The heat of adsorption per mole adsorbate subsequently remained approximately constant until the total adsorbed water was approximately 0.07 moles water / 100 g solid. Thereafter the heat of adsorption increased slightly and remained at this level (figures 10.2 and 10.3). This suggests the presence of highly energetic adsorption sites on or within the samples which were filled by approximately 0.05 moles of water / 100 g MCC, and that the adsorption sites filled between a total adsorbed water of between approximately 0.07 and 0.14 moles / 100 g MCC were approximately energetically homogeneous. The present results are not consistent with the conclusions of Hollenbeck et al (1978) for adsorption of water by Avicel PH-101. The latter workers suggested that the linearity of the heats of wetting of samples of MCC containing various amounts of adsorbed and desorbed moisture versus sample moisture content up to a moisture content of approximately 3 $\%^{w}/_{w}$ (corresponding to approximately 0.17 moles water / 100 g solid) was indicative of an energetically homogeneous surface for adsorption of water onto MCC. However, the results presented by Hollenbeck et al (1978) show that the first 0.01 mole water adsorbed by MCC has a higher differential heat of adsorption than that for subsequent adsorbed water between 0.02 and 0.17 moles water / 100 g solid, suggesting also the presence of a number, albeit smaller than indicated by the present study, of adsorption sites which are highly energetic in comparison with adsorption sites filled between 0.02 and 0.17 moles water / 100 g solid.

In the present study, the heats of adsorption per mole adsorbed water for doses of water corresponding to a total adsorbed water concentration of between 0.07 (point x on figures 10.2 and 10.3) and 0.14 moles per 100g solid by either ungranulated or granulated MCC were found to be between 54 and 57 kJ mol^{-1} (figures 10.2 and 10.3 respectively and columns 10 and 12 in tables iii.1 and iii.2 in appendix iii). The similarity of the adsorption energy over this range for the two types of MCC samples indicated that granulation did not substantially alter the surface energetics of MCC. This suggests that the reduction in compactibility of MCC following wet granulation was not due to differences in interparticulate

bonding energy once surfaces are brought into close proximity. This is generally consistent with the conclusions from cohesive energy density measurements discussed in section 8.4 where it was found that the partial solubility parameters for ungranulated and granulated MCC were similar, which was interpreted as indicating the existence of similar surface energies. In addition, the results of the present investigation indicate that the heat of adsorption over this range was greater than the heat of liquefaction for water (44 $kJmol^{-1}$). It follows that water adsorbed onto surfaces in this range will be more tightly bound than bulk water which is in agreement with conclusions presented by Zografi et al (1984) and Sadeghnejad et al (1986) regarding water adsorption by Avicel PH-101.

Differences with respect to the heat of adsorption per mole adsorbed water as a function of water uptake between ungranulated and granulated MCC may however be observed for doses of water corresponding to less than a total of 0.07 moles water per 100 g solid (figures 10.2 and 10.3). Perhaps the most striking difference between the two samples is that equilibration of granulated MCC with the sixth dose of water vapour, corresponding to the adsorption of a dose of water at approximately 0.03 moles total adsorbed water / 100 g solid (point y in figure 10.3), resulted in a much higher heat of adsorption per mole of water adsorbed than the preceding or subsequent doses. This feature was not observed in the relevant profile for water adsorption by ungranulated MCC at approximately 0.03 moles total adsorbed water / 100g solid (figure 10.2). Possible reasons for this discrepancy between the heats of adsorption for doses 6 by ungranulated and granulated MCC are discussed in section 10.3.2 below. Suggested reasons for the apparently anomalous low heats of adsorption for doses 6, 11 and 14 by ungranulated MCC (figure 10.2) and for dose 13 by granulated MCC (figure 10.3) are discussed in section 10.3.3 below.

10.3.2 Differences between the heats of adsorption for ungranulated and granulated MCC

The heat evolved (calorimeter signal), normalised to yield identical maximal heat evolved as a result of adsorption with each dose of water vapour (doses differed from each other in volume), as a function of time for individual adsorption processes by granulated MCC are shown in figures 10.4, 10.5 and 10.6.

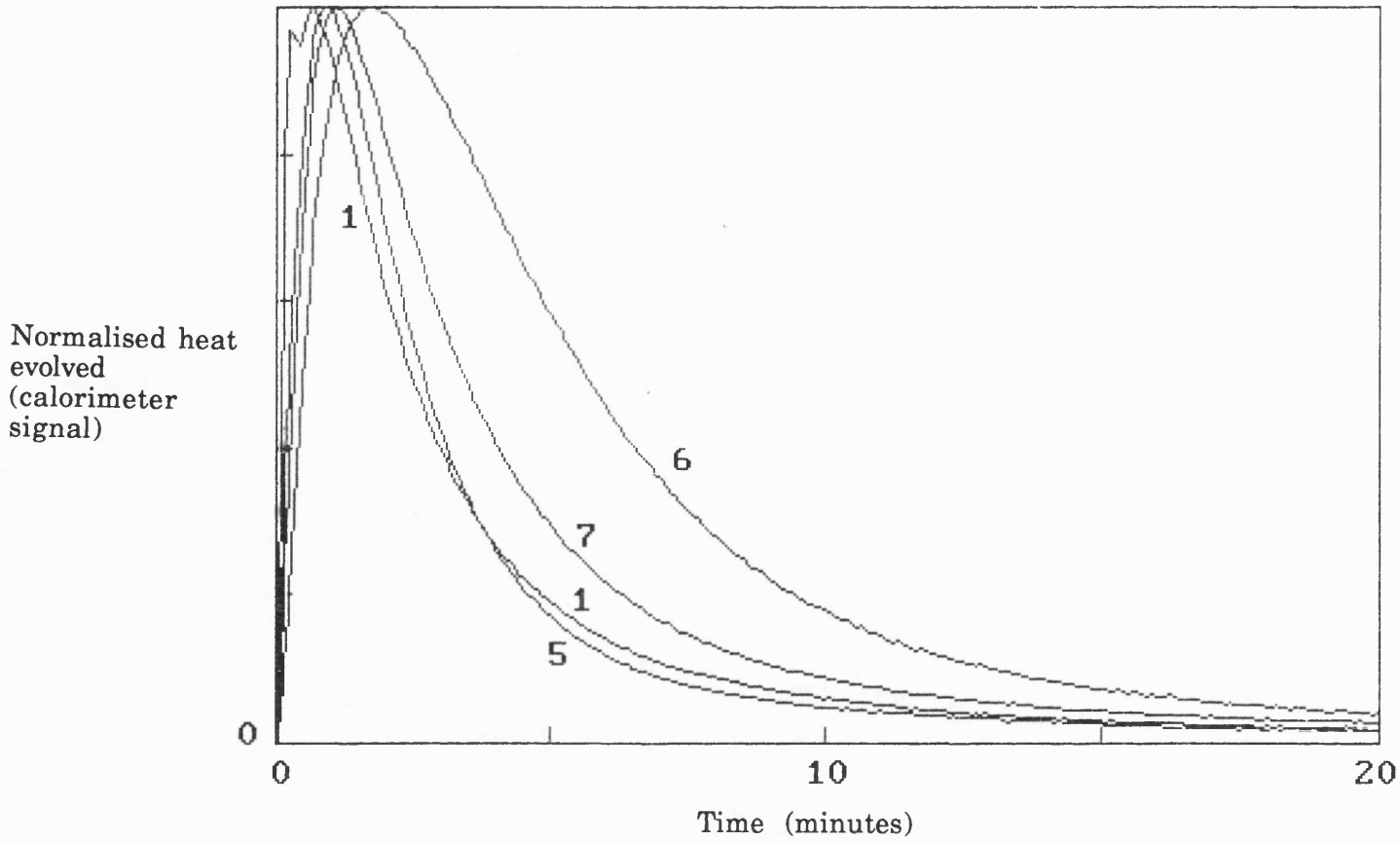


Figure 10.4 Normalised heat evolved during adsorption of doses of water as a function of time for granulated MCC.
Note: The number associated with each curve represent the dose number.

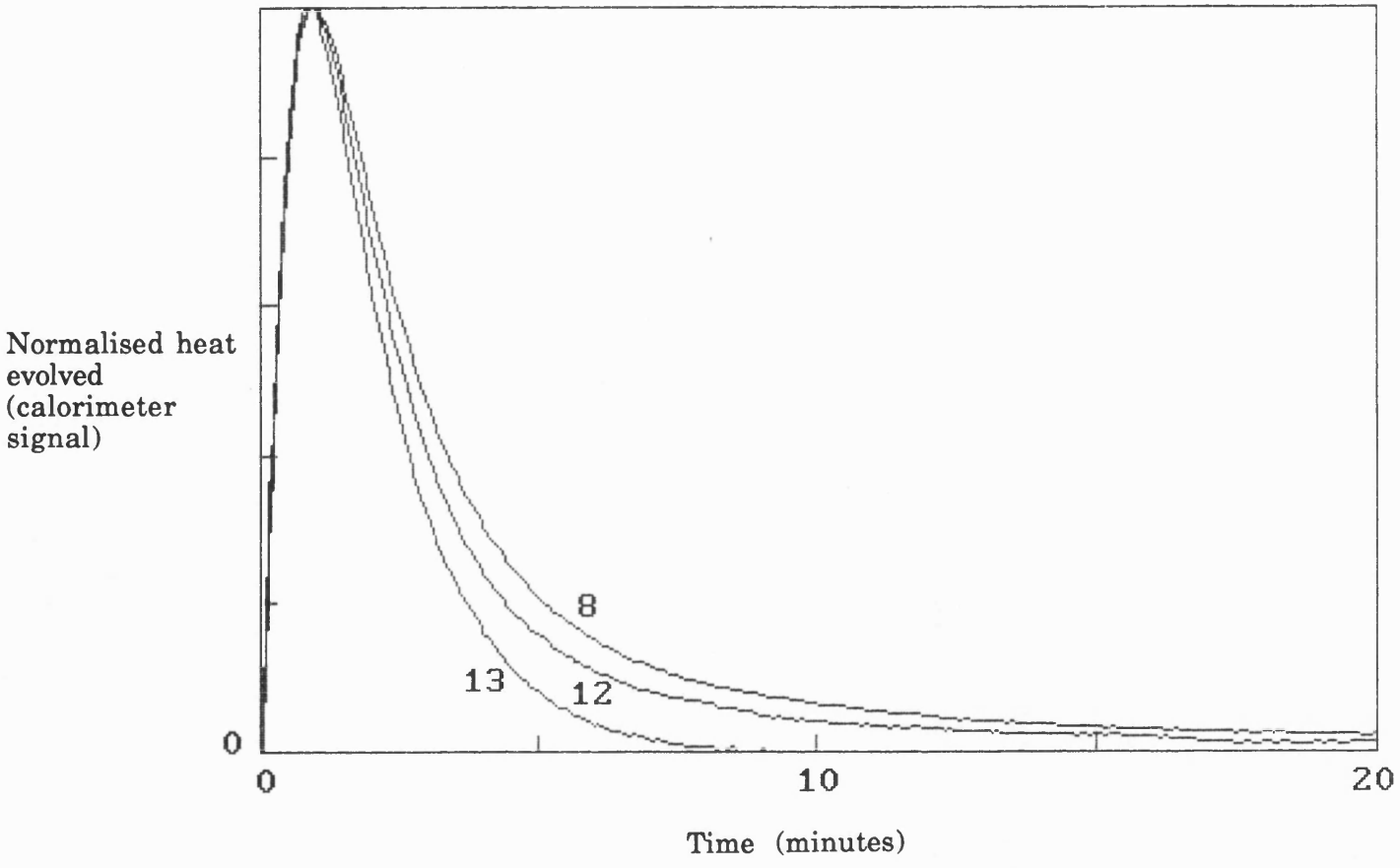


Figure 10.5 Normalised heat evolved during adsorption of doses of water as a function of time for granulated MCC.
Note: The number associated with each curve represent the dose number.

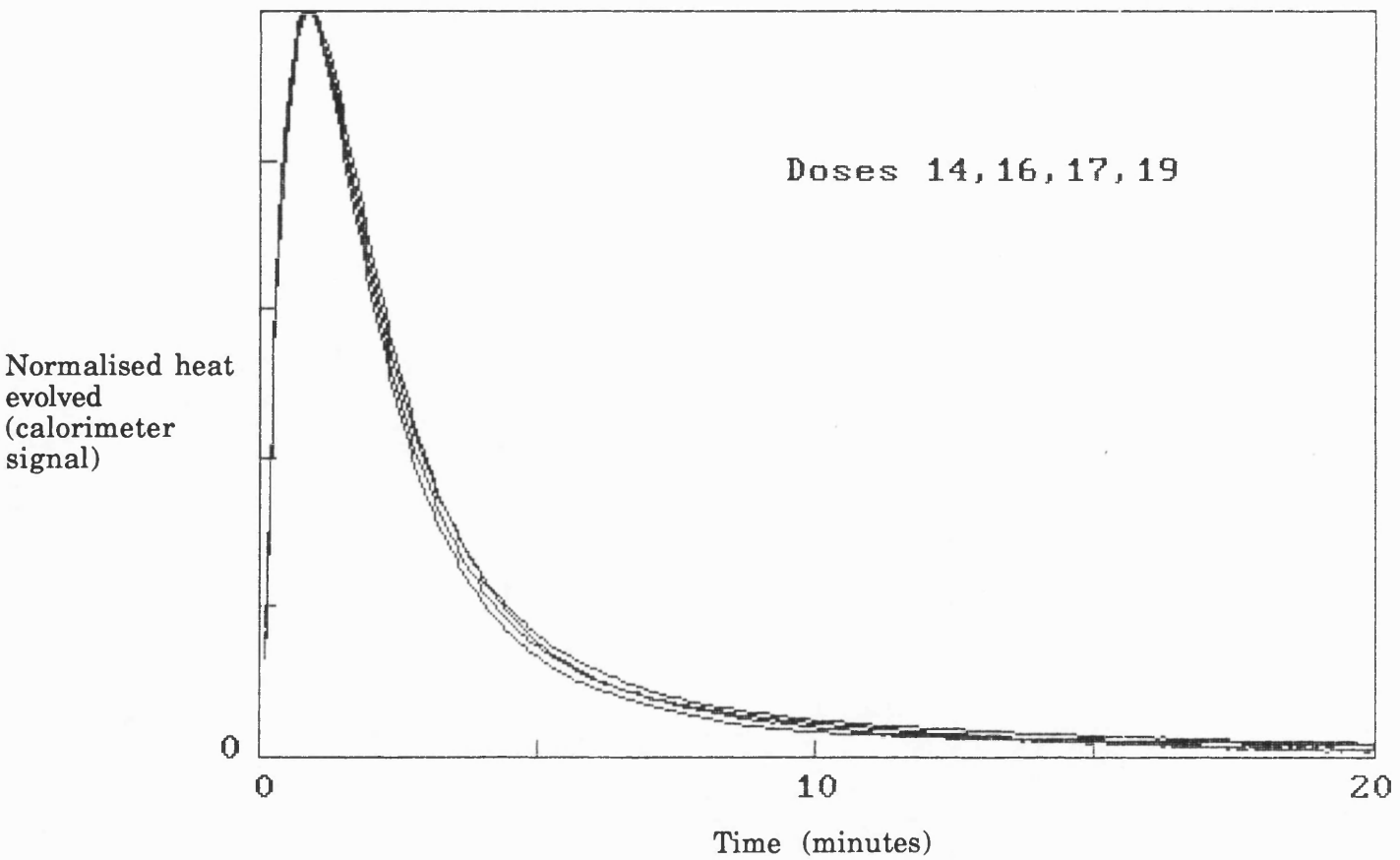


Figure 10.6 Normalised heat evolved during adsorption of doses of water as a function of time for granulated MCC.
Note: The number associated with each curve represent the dose number.

It should be noted that the evolution of heat with time for doses 1 to 5 were similar, so for clarity only curves representing adsorption of doses 1 and 5 are shown in figure 10.4. The evolution of heat during equilibration with dose 6, which as stated above was performed after leaving the sample overnight in the calorimeter cell, was substantially slower than for equilibration with dose 5 (the last dose of the previous day) (figure 10.4). The rate of evolution of heat during equilibration with dose 7 of water vapour and the sample was intermediate between that of doses 5 and 6 (figure 10.4). Equilibration of the sample with doses 8 to 12 inclusive, which were performed on the same day as each other, resulted in similar rates of evolution of heat as occurred with doses 1 to 5 (comparison between figures 10.4 and 10.5), although as the amount of water adsorbed was successively increased the rates of evolution of heat increased slightly between doses 8 to 12. Only the curves representing the evolution of heat with time corresponding to equilibration for doses 8 and 12 are shown in figure 10.5. After leaving the sample overnight, equilibration with dose 13 was found to be faster than the last dose of the previous day (dose 12) (figure 10.5), which was the reverse of the process observed between doses 5 and 6 described above. The rate of evolution of heat for dose 14 was similar to that for dose 12 (comparison between figures 10.5 and 10.6), the rate of evolution of heat with time for doses 14 to 19 inclusive was also approximately similar. Only the curves representing evolution of heat with time for equilibration with doses 14, 16, 17 and 19 are shown in figure 10.6.

A typical curve showing pressure gauge output as a function of time, with the time axis expanded for clarity, is shown in figure 10.7. The first portion of the curve during which the pressure increased (period a, figure 10.7) was due to the introduction of water vapour into the space between taps C and D. The reduction of pressure in the next portion of the curve (period b, figure 10.7) was due to water adsorption by the glass tube walls in the dead space between taps C and D. Opening of tap D to the sample resulted in a marked reduction in pressure (period c, figure 10.7), some of the reduction in pressure being due to expansion of water vapour into the sample tube and some due to adsorption on the sample surfaces. Differences in the rate of pressure decrease between samples may be assumed to be due to differences between the rate of adsorption since the rate of expansion should be approximately consistent for different doses.

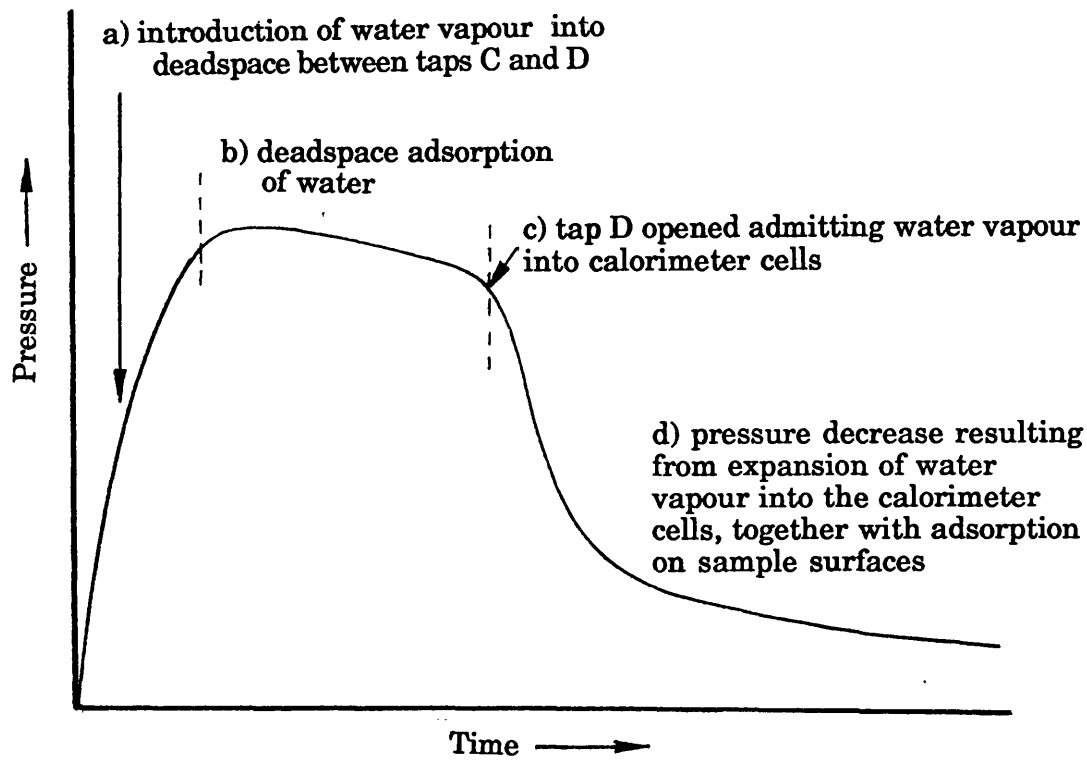


Figure 10.7 Typical curve for pressure gauge output as a function of time showing the pressure changes associated with different processes.

The change in pressure with time for doses supplied to granulated MCC for doses 1 to 13 inclusive are shown in figure 10.8. Although not conclusive, the rate at which the pressure dropped due to sample adsorption, that is the rate at which moisture was taken up by the sample, appeared to be slower for doses 6 and 7 in comparison with doses 1 to 5 (figure 10.8). Thus, following overnight storage of the sample in the calorimeter cell, the reduction in the rate of evolution of heat following overnight storage of the sample before equilibration with the sixth and seventh doses discussed above were associated with a reduction in the rate at which water was adsorbed by the sample.

Considering adsorption of dose 6 by ungranulated MCC which also occurred following overnight storage of the sample in the calorimeter cell with water vapour present in the head space, the heat of adsorption per mole was lower than for dose 5 (figure 10.2 and discussed in section 10.3.2 below) and not higher as occurred for granulated MCC (figure 10.3). Further, unlike granulated MCC, in the case of ungranulated MCC the rate of evolution of heat (figure 10.9) and the rate of pressure decrease (figure 10.11) was similar for doses 5 and 6.

A possible explanation for the higher heat of adsorption per mole adsorbed water (figure 10.3) together with the reductions in the rates of evolution of heat (figure 10.4) and moisture adsorption (figure 10.8) during sample equilibration with dose 6 in comparison with doses 1 to 5 by granulated MCC is developed immediately below.

It is suggested that when the sample of granulated MCC was left overnight in the calorimeter cell following equilibration with dose 5 (at a relative pressure of 0.0125), additional sites available for water adsorption may have been created. The latter may have arisen from disruption of hydrogen bonding between cellulose surfaces within granules by adsorbed / adsorbing water molecules. This would facilitate deeper penetration of water vapour into the granules. One of two processes may occur; a) if the previously adsorbed water molecules are bound with a comparatively low energy, it may be expected that the newly created highly energetic sites would be filled by rearrangement of adsorbed molecules of water resulting in the availability of previously filled lower energy sites on the sample surfaces, or b) if the previously adsorbed water is highly bound, rearrangement of adsorbed water molecules will be less likely. In either of the above cases, during overnight storage, adsorption of additional water vapour by the sample from the

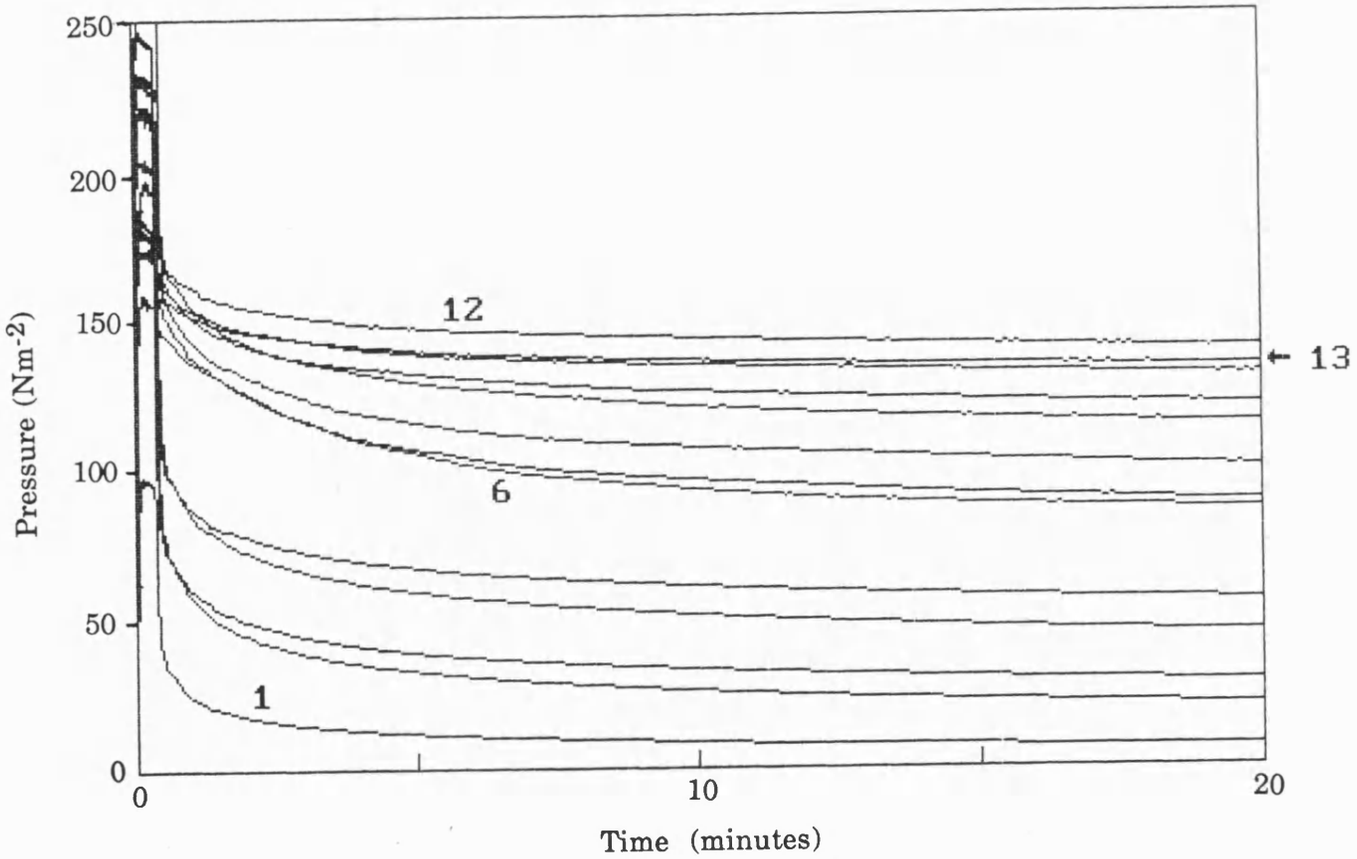


Figure 10.8 Pressure gauge output as a function of time for equilibration of successive doses of water vapour with granulated MCC.
Note: Selected curves are numbered with the dose number and, in general, as the dose number increases, the approximately linear portion of the pressure signal curve is displaced up the y-axis, the exception being the pressure signal associated with dose 13 which is lower than that for dose 12.

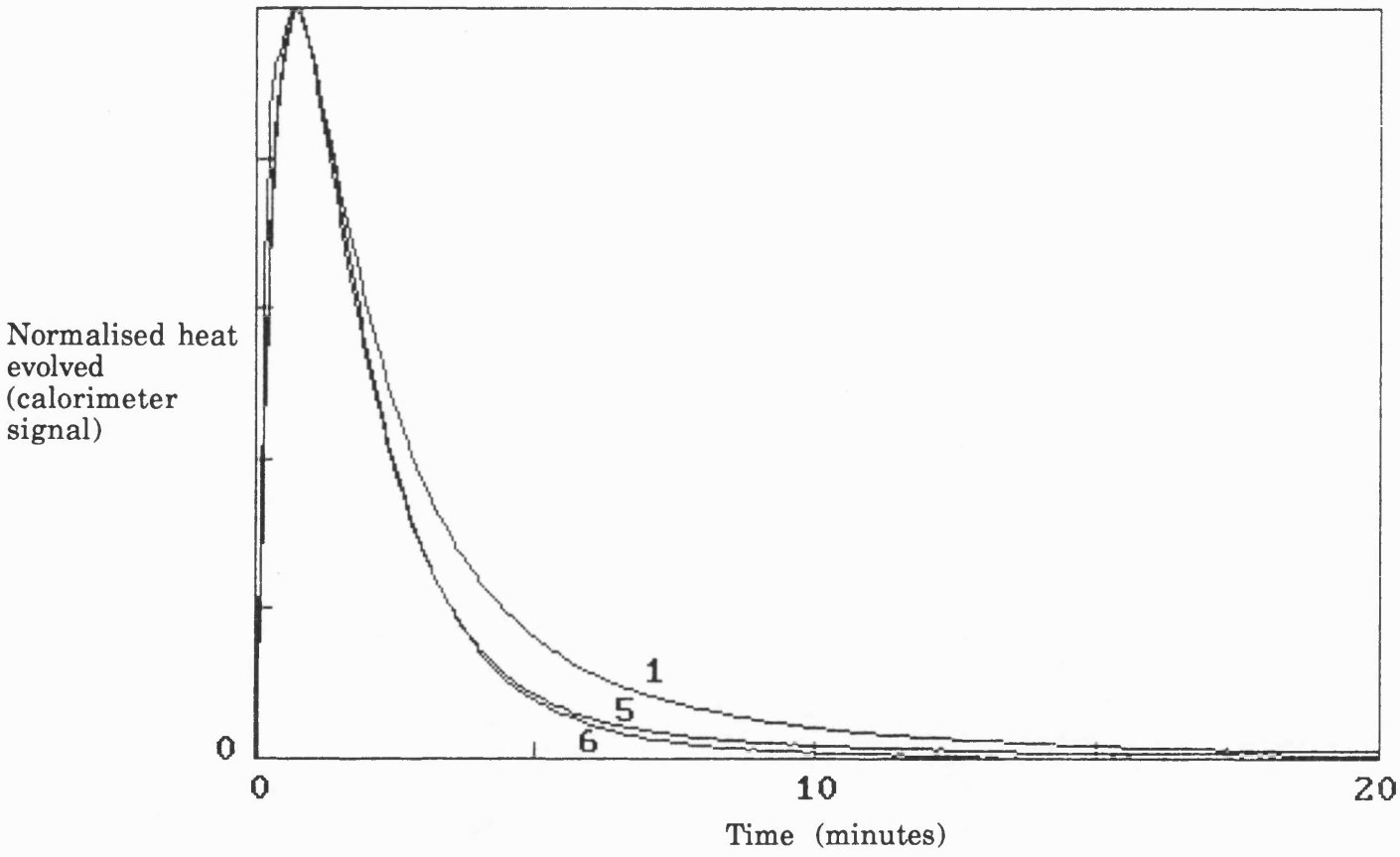


Figure 10.9 Normalised heat evolved during adsorption of doses of water as a function of time for ungranulated MCC.
Note: The number associated with each curve represent the dose number.

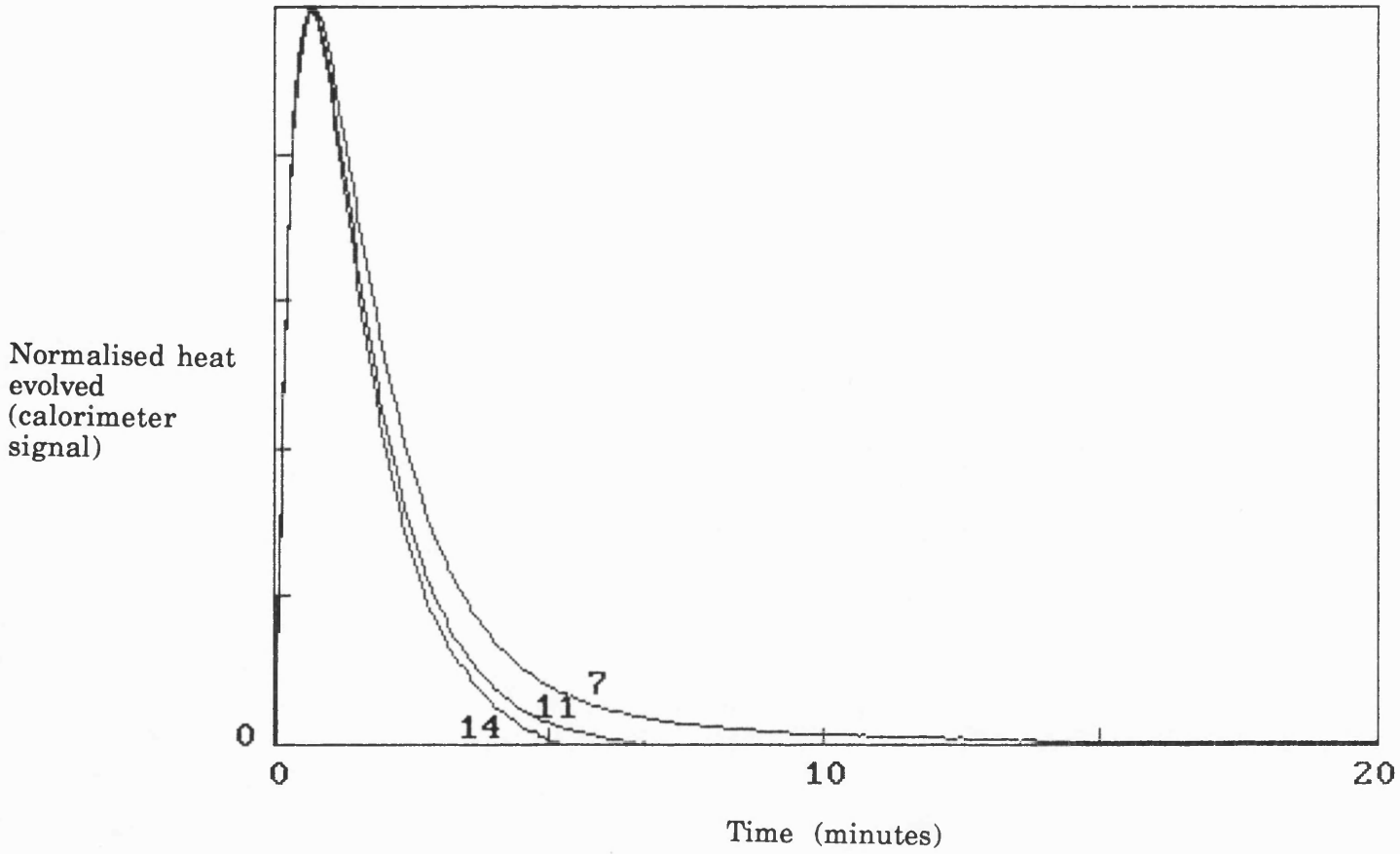


Figure 10.10 Normalised heat evolved during adsorption of doses of water as a function of time for ungranulated MCC.
Note: The number associated with each curve represent the dose number.

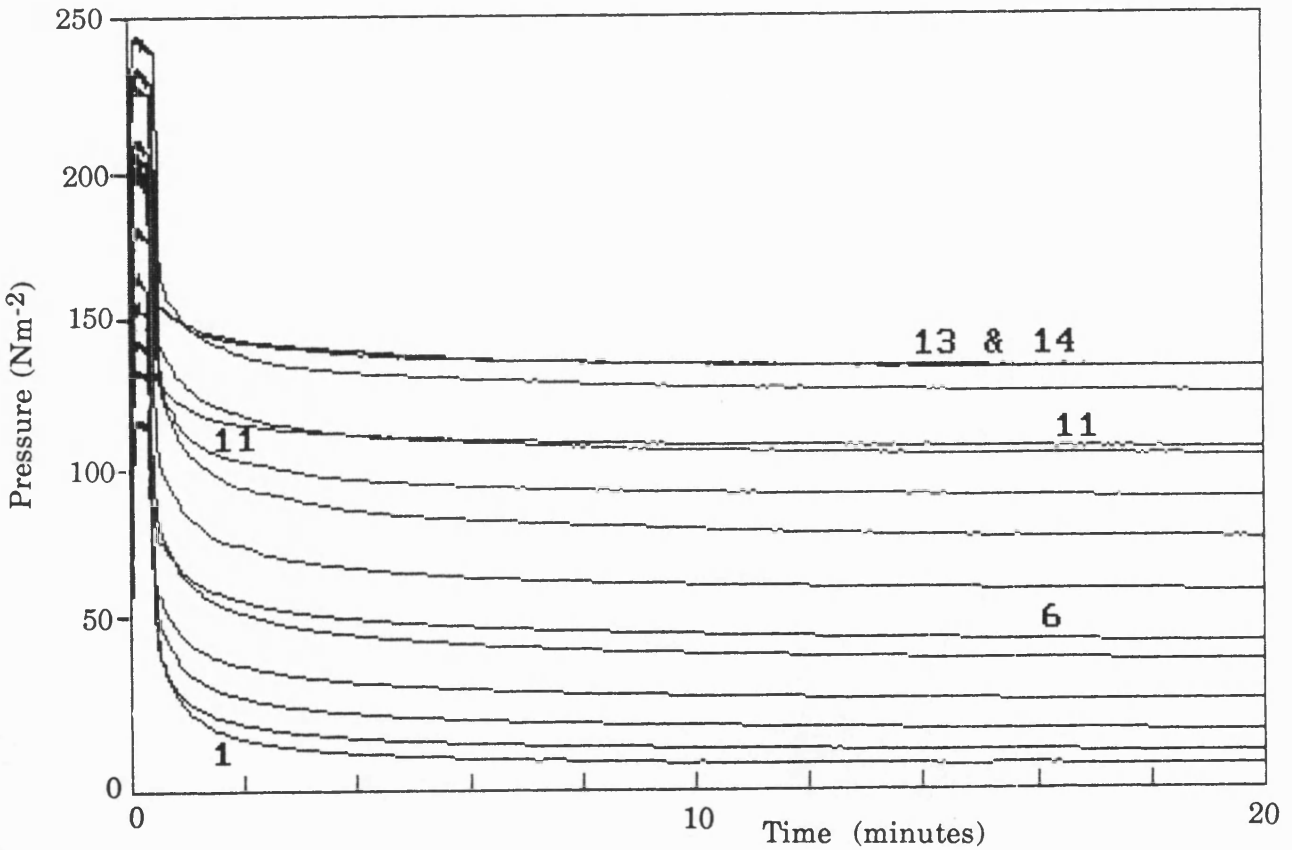


Figure 10.11 Pressure gauge output as a function of time for equilibration of successive doses of water vapour with ungranulated MCC.
Note: Selected curves are numbered with the dose number and, in general, as the dose number increases, the approximately linear portion of the pressure signal curve is displaced up the y-axis.

headspace might be expected, although the latter could not be investigated directly with the present methodology. As explained in greater detail below, correction of the heat of adsorption per mole adsorbate for dose 6 by granulated MCC from consideration of the errors associated with the remainder volume after overnight equilibration with dose 5 would lead to the actual heat of adsorption per mole adsorbate for dose 6 being even higher than shown in figure 10.3. Hence, overnight adsorption of an unquantified amount of water would not directly account for the unexpectedly high heat of adsorption per mole adsorbate for dose 6 by granulated MCC. In addition, no attempt was made to directly quantify the energy associated with bond disruption and formation in the calorimeter overnight since it was considered that the latter processes could be expected to occur more slowly than would be measurable to an acceptable degree of accuracy. Furthermore, either of the above cases a) or b) may be expected to result in the creation of adsorption sites which may be filled at higher relative pressures which followed overnight equilibration in the calorimeter cell. However, since equilibration of the sample of granulated MCC with the first dose of the next day (dose 6) resulted in a higher heat of adsorption per mole of adsorbed water than occurred as a result of adsorption of the first dose of water, it was considered more likely that process b) rather than process a) described above occurred as a result of overnight sample storage. This was because in the case of process a), adsorption at previously filled energy sites would be expected to occur at similar or lower heats of adsorption per mole to those for the first water dose, which was not found. The kinetics for the adsorption process and for the evolution of heat provide further evidence to support interpretation b) above since the slower evolution of heat and water uptake as a result of sample equilibration with dose 6 in comparison with equilibration with doses 1 to 5 suggests that the activation energy of the adsorption sites filled by dose 6 was higher than for adsorption sites filled during doses 1 to 5.

As mentioned briefly above, the adsorption of a directly unquantified amount of water from the headspace during overnight storage of the sample in the calorimeter cell between doses 5 and 6 would render the calculated remainder volume (appendix iii, section iii.1) following sample equilibration with dose 5 being higher than that actually present immediately prior to sample equilibration with dose 6. Thus, the calculated adsorbed volume of water following sample equilibration with dose 6 would be incorrectly high. This would result in an erroneously reduced calculated heat of adsorption per mole adsorbed water for

dose 6. In addition, the adsorption of an unknown amount of additional water vapour between doses 5 and 6 renders the total amount of water vapour adsorbed per 100 g MCC as a result of equilibration with further doses consistently incorrectly low. Therefore the bars representing the heat of adsorption of water by granulated MCC in figure 10.3. for doses 6 and above should by displaced by a constant, but from the above discussion, unknown amount, along the x-axis. Estimation of this error is discussed in section 10.3.4 below.

The kinetic data for the pressure change (figure 10.8) and heat evolved (figure 10.4) during adsorption processes also suggest that adsorption onto the high energy sites created as discussed above between doses 5 and 6 continued during adsorption of dose 7, but was complete before adsorption of dose 8. However, unlike dose 6, adsorption of dose 7 appeared not to be associated with a higher heat of adsorption per mole adsorbed water (figure 10.3). Adsorption of further doses of water vapour and leaving the sample overnight again between doses 12 and 13 did not appear to result in a similar phenomena to that occurring between doses 5 and 6 which, as discussed above, was suggested to be due to the creation of additional adsorption sites. In fact, the heat of adsorption per mole water was lower for dose 13 in comparison to dose 12 (figure 10.3). Further, although inconclusive, the rate of evolution of heat as a result of the addition of dose 13 appeared to be faster than for dose 12 (figure 10.8). Adsorption of dose 13 by granulated MCC is discussed further in section 10.3.3 below.

The phenomenon occurring after overnight storage of the sample in the presence of water vapour between doses 5 and 6 appears to be unique to granulated MCC since it was not observed for water vapour adsorption on to ungranulated MCC, and does not appear to have been reported for other materials using similar methodology. In addition, it was considered that the occurrence of this phenomena for granulated MCC but not for ungranulated MCC was due to granulation resulting in an increase in the amount of hydrogen bonding between cellulose microcrystals within particles in comparison with ungranulated MCC. On adsorption of water vapour these bonds were disrupted. This supports the theory proposed in section 3.4.1 for granulation of MCC causing intraparticulate bonding by quasi-hornification, and is consistent with the similarity of the water adsorption isotherms for ungranulated and granulated MCC (Chapter 9). Unfortunately the significance of the results are unknown since replicate determinations were not performed. The hypothesis presented above should be tested further by using constant outgassing intervals between successive doses.

10.3.3 Discussion of the unexpectedly low heats of adsorption observed as a result of equilibration of ungranulated and granulated MCC with some water vapour doses

It was noted that equilibration of doses 11 and 14 and perhaps dose 6 of water vapour with ungranulated MCC resulted in substantially lower heats of adsorption than might be anticipated from the heat evolved for other water vapour doses (figure 10.2). Similarly the heat evolved during adsorption of dose 13 and perhaps dose 10 by granulated MCC was lower than anticipated from data for the other doses (figure 10.3). Furthermore, the heat of adsorption of doses 11 and 14 by ungranulated MCC and dose 13 by granulated MCC was lower than the heat of liquefaction of water (figure 10.2 and 10.3). From consideration of the kinetic data for heats of adsorption and vapour pressures for these adsorption processes, the origin of these comparatively endothermic adsorption processes is discussed below.

Heats evolved as a function of time for selected doses by ungranulated MCC are shown in figures 10.9 and 10.10. Water vapour adsorption was slightly faster for dose 1 than for dose 2 and the evolution of heat for adsorption of doses 3, 4 and 5 were similar to that for dose 2, equilibration with dose 6 being marginally slower. For clarity only the curves for doses 1, 5 and 6 are shown in figure 10.9. The rate of evolution of heat after equilibration of dose 7 (figure 10.10) of water vapour with the sample was similar to that for dose 5 (comparison of figure 10.10 with 10.9). Equilibration of the sample with doses 8, 9, 10, 12 and 13 resulted in similar rates of evolution of heat as observed for adsorption of dose 7 of water, although the rate of evolution became slightly faster as the amount of water adsorbed was increased. However, the rate of evolution of heat for equilibration with dose 11, which was supplied after an evacuation time of 2 hours rather than between 10 and 15 minutes (as was the case of the majority of other doses), was slightly faster than that for dose 10. Likewise, the rate of evolution of heat as a result of adsorption of dose 14, which was supplied after leaving the sample overnight, was faster than for dose 13 of the previous day. The curves for doses 7 and 11 and 14 only are shown in figure 10.10. With the exception of doses 3, 6, 11, and 14, all doses were supplied after a maximum of 10 minutes evacuation, doses 6, 11 and 14 yielding comparatively endothermic heats of adsorption (figure 10.2). In addition, although not conclusive, the rates of water

uptake as assesed using the pressure curves for doses 6, 11 and 14 are perhaps slower than for the other doses (figure 10.11). Considering the adsorption of doses of water vapour by granulated MCC, the adsorption process for dose 13 which was performed after overnight storage of the sample in the calorimeter, together with prolonged evacuation resulted in a slower adsorption process as indicated by both kinetic data for the evolution of heat (figure 10.5) and vapour pressure (figure 10.8).

Closer inspection of the calorimeter output as a function of time revealed that for doses 11, and 14 (figure 10.10), and perhaps dose 6 (figure 10.9) of water adsorbed by ungranulated MCC, and dose 13 (figure 10.5) of water adsorbed by granulated MCC, the calorimeter output following apparent completion of the adsorption process was less than the baseline output before addition of adsorbed water vapour. Although this may be due to experimental error, it was considered potentially significant that amongst other doses, this phenomenon was observed for the first doses added to both ungranulated and granulated MCC after the second sample was stored overnight in the calorimeter cell. During overnight storage the deadspace between taps C and D was continuously evacuated. Thus, moisture adsorbed on the glass tube walls in this region will be removed. It is possible that when the first dose of water vapour was admitted to the space between taps C and D the following day, water adsorption onto these deadspace surfaces was incomplete before the dose was admitted to the calorimeter cells. Thus, it is proposed that further water uptake by the tubespace may occur simultaneously with water adsorption by the sample. This would result in the amount of water adsorbed as determined from the pressure readings being erroneously high by a factor corresponding to the pressure value due to the amount of water taken up by the glassware between taps C and D after opening tap D. Further, the calculated adsorption per mole adsorbed water obtained for that dose would be erroneously low, although the determined heat of adsorption for the amount of water vapour actually adsorbed would be correct. The reduction in the calorimeter output following completion of the adsorption process for these doses to below the baseline value further suggests that some of the adsorbed sample water is desorbed to equilibrate the space in the tubes; balancing the moisture adsorbed onto the glassware would result in energy being consumed in the calorimeter cell which would explain the final calorimeter signal being lower than before the water vapour was admitted to the sample. It may be expected that

desorption from the sample to the glassware may occur more readily at higher levels in comparison with lower levels of adsorbed moisture since at higher adsorbed water levels the heat of adsorption was lower; hence the reduction in heat evolved in comparison with that expected is greater for dose 13 than for dose 6 for ungranulated MCC. The reason for the comparatively endothermic adsorption for dose 11 by ungranulated MCC and dose 10 by granulated MCC may be due to a similar phenomenon since before these doses were introduced, the system had been left outgassing for approximately 1.5 hours. Furthermore, since the latter phenomenon occurred for dose 6 in the case of ungranulated MCC, that is immediately after overnight storage, it is proposed that the heat of adsorption for dose 6 by granulated MCC should be even higher than is shown in figure 10.3 if the phenomenon described due to incomplete adsorption by the deadspace glassware is taken into consideration.

The hypothesis proposed to explain the phenomena discussed in this section may readily be tested by comparison of the existing data with that obtained whilst maintaining constant outgassing intervals for the deadspace. In addition, if the hypothesis is proved correct, it may be desirable to maintain constant apparatus outgassing intervals between successive doses supplied to samples in future studies. However, the interesting phenomenon discussed in section 10.3.2 may not have been observed if constant outgassing intervals had been used. To test the hypothesis, separate experimental protocols would be desirable.

10.3.4 Surface area analysis using water adsorption isotherms

The adsorption isotherms for granulated and ungranulated MCC are shown in figures 10.12 and 10.13 respectively. The isotherm for ungranulated MCC obtained is broadly similar to those obtained using a different commercial form of MCC (Avicel PH-101) by Hollenbeck et al (1978), Sadeghnejad et al (1986), and Parker (1989) at similar relative pressures. At water vapour relative pressures greater than 5 %, the amount of water adsorbed onto MCC surfaces increased approximately linearly with relative vapour pressure (figures 10.12 and 10.13). However, in the present study, differences were observed between isotherms for ungranulated and granulated MCC at a relative pressure of approximately 0.02, corresponding to a total adsorbed volume of approximately 0.03 moles water / 100 g solid. At this relative pressure the volume adsorbed by granulated MCC as

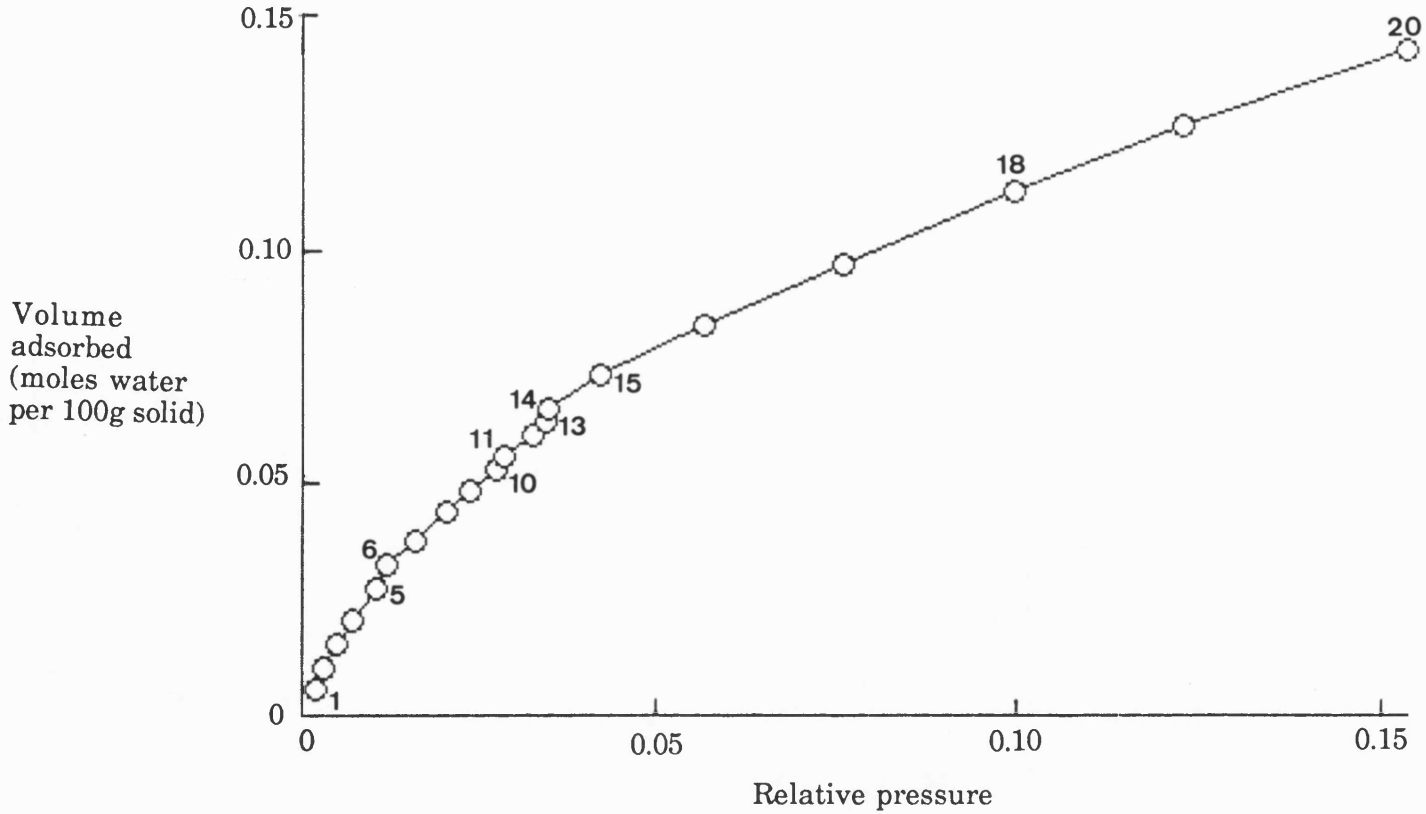


Figure 10.12 Adsorption isotherm for water vapour by ungranulated MCC
Note: Selected points are numbered with the dose number.

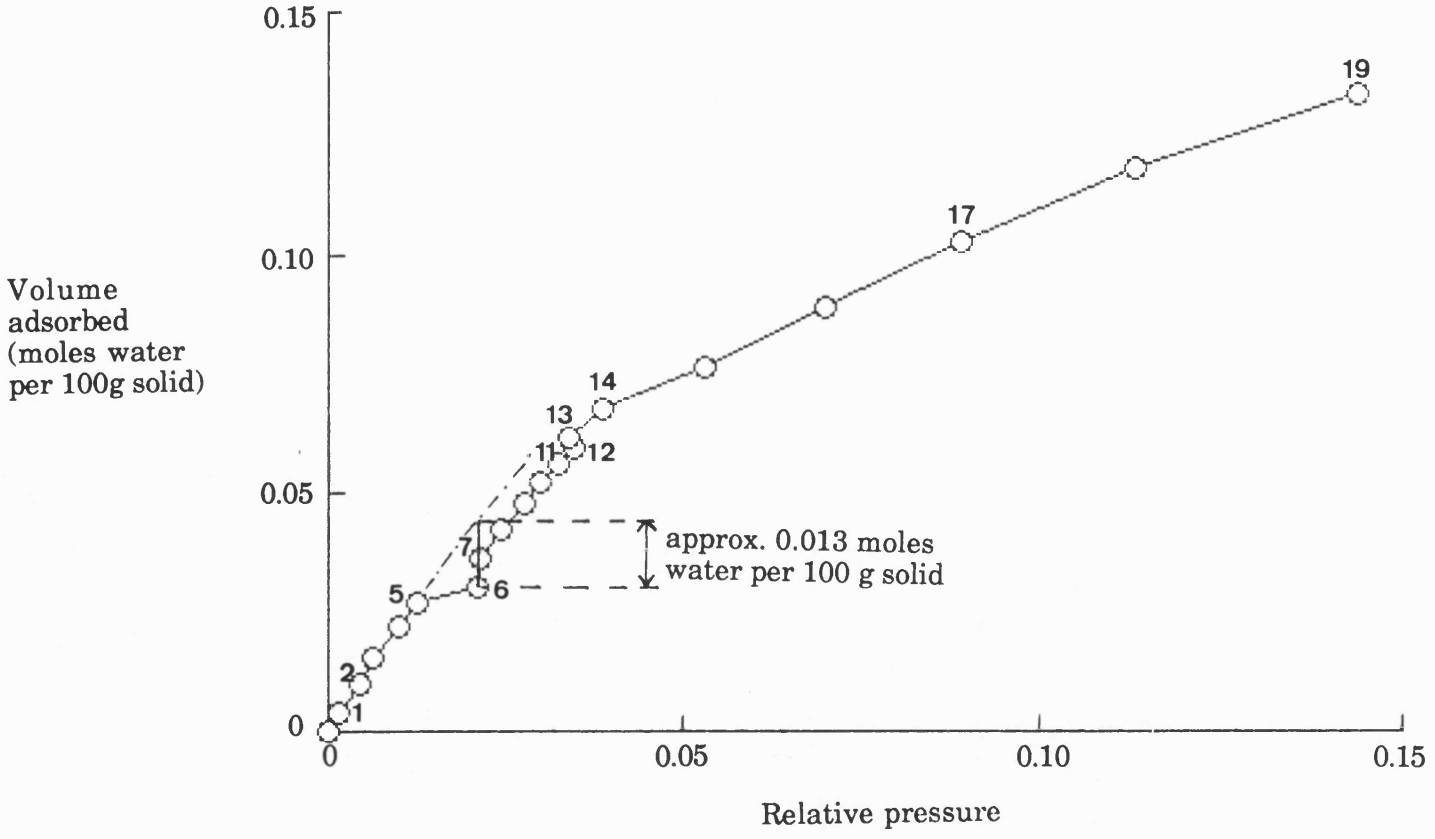


Figure 10.13 Adsorption isotherm for water vapour by granulated MCC
Note: Selected points are numbered with the dose number.

a function of the vapour pressure increased irregularly, whereas the isotherm for ungranulated MCC incresed relatively smoothly. It is considered that the irregularity in the adsorption isotherm for granulated MCC was related to the process discussed in section 10.3.2 above, and more specifically was due to water adsorption during overnight storage of the sample, the extent of which was not measured directly. Thus, as also discussed in section 10.3.2, the calculated value for the total amount of water vapour adsorbed following addition of dose 6 was less than the total amount actually adsorbed by the sample. Hence it is proposed that the points on the adsorption isotherm obtained as a result of sample equilibration with dose 6 and higher doses would be displaced along the y-axis by a constant amount which, by extrapolation of the isotherm from dose 5 as indicated in figure 10.14, is suggested to be approximately 0.013 moles per 100 g solid.

Closer inspection of the isotherms presented in figures 10.12 and 10.13 also reveals marginal discontinuities at volumes adsorbed corresponding to equilibration with dose 11 and 14 for ungranulated MCC, and with dose 13 for granulated MCC. The latter may be associated with the process suggested in section 10.3.3 above; more specifically, adsorption of water onto the tube walls in the deadspace resulting in an artificially high amount of water vapour adsorbed which resulted in the calculated data points for adsorption of these doses being erroneously displaced up the y-axis. The suggested artifacts in the data obtained and discussed in section 10.3.3 would also result in the cumulative amounts adsorbed for doses after which this process occurred being incorrectly high.

The B.E.T. relationship described in section 1.5.4.6 was used to estimate the surface area of ungranulated and granulated MCC available for water adsorption from the amount of water adsorbed at relative pressures greater than 0.05 (columns 9 and 13 in tables iii.1 and iii.2 in appendix iii and presented in tables 10.1 and 10.2 below). The equation was modified so that the weight of water adsorbed after each dose was expressed in terms of weight adsorbate per gram of solid. However, it was recognised that the errors discussed previously in this section and which are associated with the volumes adsorbed at relative vapour pressures greater than 5 % limit the accuracy of such determinations. The B.E.T. equation data for water adsorption by ungranulated and granulated MCC is provided in tables 10.1 and 10.2 respectively.

Table 10.1. B.E.T. data for adsorption of water vapour by ungranulated MCC

Dose	Water (μmol) adsorbed by 0.0972 g solid	Total mass adsorbed, W' (g water per g solid)	Relative vapour pressure, P/P_o	$\frac{P/P_o}{W'(1-P/P_o)}$
16	80.80	0.0149	0.0558	3.950
17	93.66	0.0173	0.0754	4.702
18	109.1	0.0202	0.0989	5.433
19	122.5	0.0227	0.1222	6.133
20	138.4	0.0256	0.1530	7.056

Table 10.2. B.E.T. data for adsorption of water vapour by granulated MCC

Dose	Water (μmol) adsorbed by 0.0996 g solid	Total mass adsorbed, W' (g water per g solid)	Relative vapour pressure, P/P_o	$\frac{P/P_o}{W'(1-P/P_o)}$
15	76.25	0.0138	0.0524	4.007
16	88.48	0.0160	0.0691	4.639
17	102.37	0.0185	0.0879	5.209
18	117.54	0.0212	0.1121	5.955
19	132.90	0.0240	0.1426	6.930

The adsorption data were plotted using a linear form of the B.E.T. equation and are shown in figures 10.14 and 10.15 for ungranulated and granulated MCC respectively. Also given in figures 10.14 and 10.15 are the gradients and intercepts of the graphs. The derived values of the volume adsorbed at monolayer capacity and the specific surface area, determined using the relationships presented in section 1.5.4.6 are given in table 10.3.

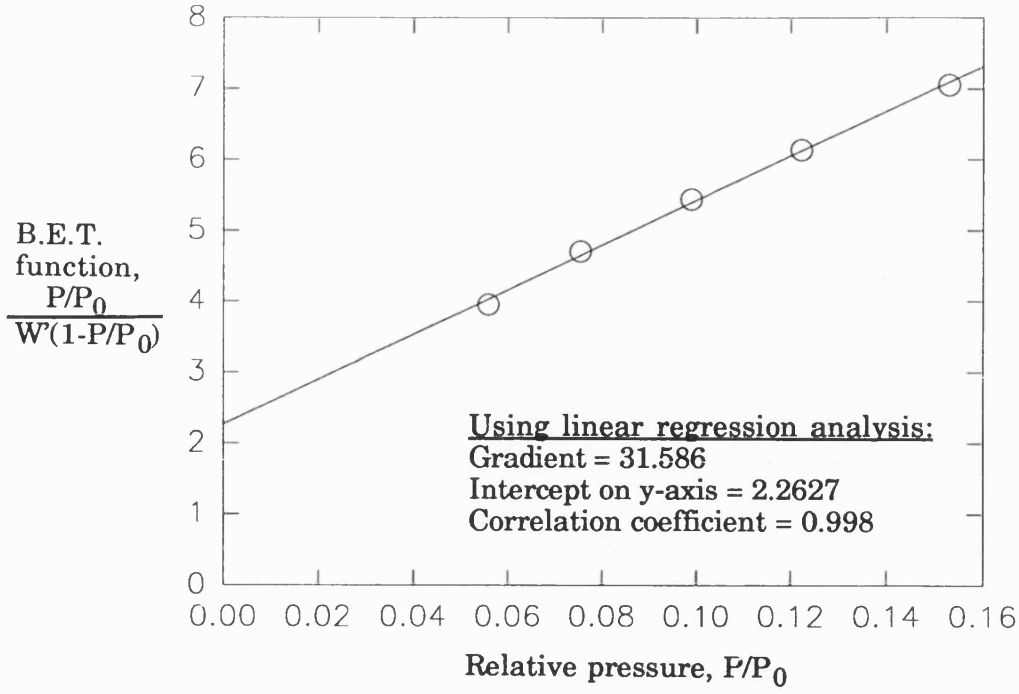


Figure 10.14 B.E.T. plot showing adsorption of water vapour by ungranulated MCC

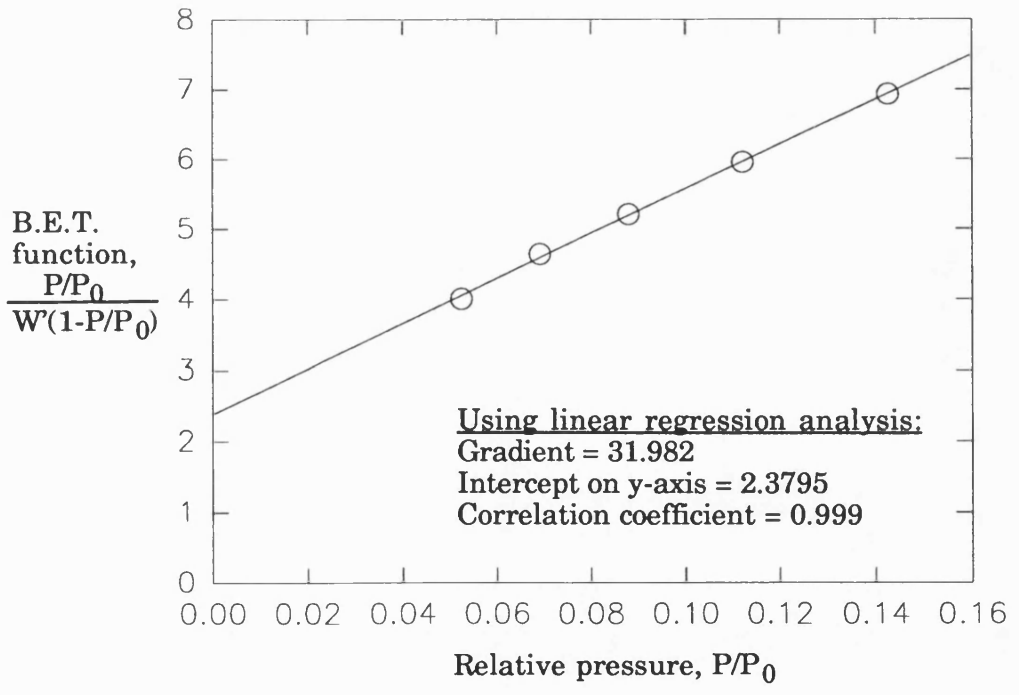


Figure 10.15 B.E.T. plot showing adsorption of water vapour by granulated MCC

Table 10.3 B.E.T. surface area data for ungranulated and granulated MCC from water vapour adsorption data

Material	Monolayer Capacity (g water / g solid)	Specific Surface area (m^2g^{-1})
Ungranulated MCC	0.0295	106.5
Granulated MCC	0.0291	105.1

Correlation coefficients obtained by linear regression analyses, together with visual inspection of the plots indicated reasonably close correlation to the linear form of the B.E.T. equation. The monolayer capacities for the two MCC samples studied are shown in table 10.3 and were found to be similar for ungranulated and granulated samples. This is in contrast to the B.E.T. determinations carried out using nitrogen as the adsorbate gas where the specific surface area of granulated MCC was found to be approximately one-third the surface area available for nitrogen adsorption on ungranulated MCC (section 3.3.1). Surface areas determined using water adsorption data were approximately 100 times greater than those determined using nitrogen adsorption, a phenomenon which has been reported previously and is discussed in section 1.5.4.6. Furthermore, the mass of water adsorbed at monolayer coverage was in approximate agreement with the monolayer capacities suggested for Avicel PH-101 by Hollenbeck et al (1978) (0.033 g water / g solid), Nakai et al (1977) (0.0350 g water / g solid), and Parker (1989) (0.0375 g water / g solid).

Chapter 11. A study of the effect of wet granulation and commercial source on the polymorphic form and degree of crystallinity of MCC

11.1 Aims and Objectives

As discussed in section 1.3.1, cellulose is an aperiodic polymorphic solid having mixed crystal lattices as well as 'amorphous' forms. Polytypic forms of cellulose exhibit different chain conformations, intermolecular interactions and chain packing modes.

The principle objective of the following study was to investigate the effect of wet granulation on the polymorphic form of one commercial form of MCC using a number of different analytical methods. Another objective of the study was to investigate whether different commercial forms of MCC differed with respect to their polymorphic form and / or degree of crystallinity, thus perhaps contributing to differences reported by other workers with respect to their relative compactibilities.

11.2 Materials

The commercial forms of MCC investigated together with their batch numbers are listed in table 11.1. MCC granules were prepared batchwise according to the general method described in section 3.2.1 using 150 g MCC (Emcocel 50M, lot number 8261, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) and 105 g distilled water, which corresponded to 41.2 $\%^{w}/_{w}$ water in the final wet mass, and dried using the method described in section 3.2.2. Ungranulated and granulated MCC were separated according to sieve diameters using the method described in section 2.2.1. In all the analyses described below 45 - 63 μm sieve fractions were used.

11.3 Methods

11.3.1 Powder X-ray diffractometry and estimation of degree of crystallinity

Powder X-ray diffractograms were obtained using the equipment described in section 3.2.5. The percentage of crystalline material, *%Cr*, was estimated from X-ray diffractograms using the method proposed by Nelson & O'Connor (1964b) described previously in equation 3.1 (Chapter 3) and shown diagrammatically in

Table 11.1 Sources of microcrystalline celluloses investigated

Commercial form and grade of MCC	Batch number	Supplier
Avicel PH-101	6547	FMC Corp., U.S.A.
Avicel PH-102	7242	FMC Corp., U.S.A.
Emcocel 50M	8261	Mendell, U.S.A.
Emcocel 90M	7019	Mendell, U.S.A.
Unimac MG-100	5175	Uniteka Rayon Co., Japan
Unimac MG-200	5125	Uniteka Rayon Co., Japan
Indocel 80	unknown	Neelkanth Chemicals, India

figure 11.1. It should be noted that the exact diffraction angle at which the 002 peak and amorphous intensities are determined varies slightly with the polymorphic form of the sample (Nelson & O'Connor, 1964b).

11.3.2 Raman spectrometry

Spectra were recorded using a FT-Raman spectrometer (Type FTA106, Bruker Spectrospin Ltd., Coventry, U.K.). The excitation source was a Nd:YAG laser operated at 1.064 μm. The incident laser power on the sample was 300 mW. The spectra were recorded at a resolution of 4 cm^{-1} using 500 accumulated scans. No sample preparation other than described in 11.2 was required. Since the radiation is pure scattering, band shapes are not distorted by optical effects such as multiple internal reflection or strong absorption which can cause difficulties in the interpretation of infra-red spectra (see section 11.3.3 below). In addition, band precision of spectra obtained using FT-Raman spectrometry is in general high and superior to that obtained using real - time Raman spectrometry. Thus, it was considered that spectra obtained could be subtracted with a high degree of accuracy. Subtraction spectra for Unimac MG-100 minus ungranulated Emcocel 50M, and for ungranulated minus granulated Emcocel 50M were generated using the associated equipment software to facilitate comparative analysis.

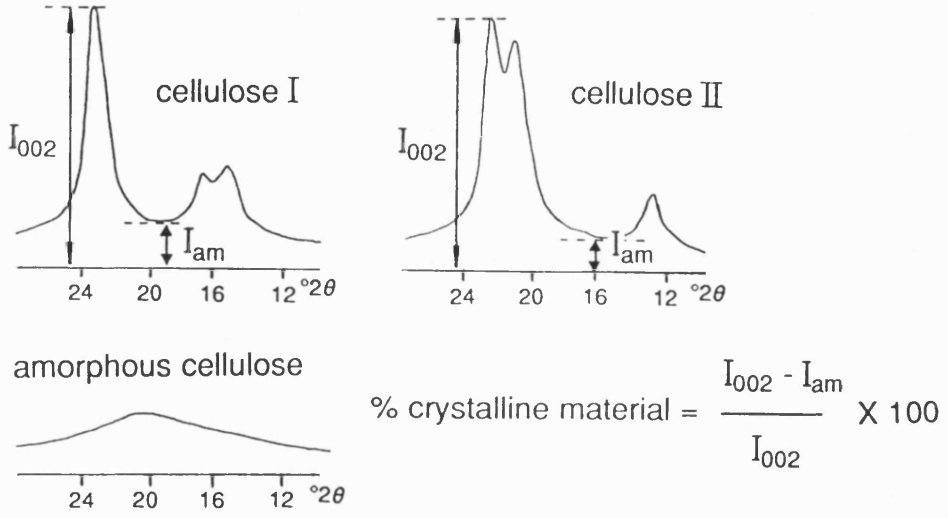


Figure 11.1 Powder X-ray diffractograms showing relevant plot intensities used in calculation of percentage crystallinity (equation 3.1), after Nelson & O'Connor (1964b).

11.3.3 Infra-red spectroscopy

Crystalline powders tend to scatter radiation strongly. Therefore generation of infra-red (IR) spectra for cellulose particles requires preparation techniques which will result in reduced scattering.

Initial IR spectroscopic analysis of bulk particles of MCC was attempted using diffuse reflectance spectroscopy of MCC diluted with dried potassium bromide. However, the spectra obtained were found to be poorly reproducible and there was some evidence of a drifting baseline, perhaps due to moisture adsorption which varied over the time during which spectra were collected. Transmission spectroscopy of pressed-disks containing MCC diluted with potassium bromide was also considered. However, it was considered that this technique has the disadvantage of requiring sample milling and compaction procedures, both of which could potentially result in an artifactual alteration of the intraparticle hydrogen bonding which may have obscured differences between ungranulated and granulated MCC. Further, it was considered that both the above IR techniques suffered from the potential disadvantage of a high degree of band distortion on the spectra produced arising from multiple interactions between the IR beam and MCC particles. Thus, diffuse reflectance and transmission IR spectroscopic methods were not considered sufficiently reproducible or accurate for use in the present study where quantification of small molecular changes was required.

11.3.3.1 Optical infra red microspectrometry

Optical IR microspectrometry is an alternative technique by which the IR spectra for individual particles can be obtained. Details of the principles of IR microspectrometry can be found elsewhere (e.g. Siesler & Holland-Moritz, 1980a). Briefly, dispersed monochromatic radiation in the IR region is focused at the sample position and the radiation transmitted by the sample focused at the detector. Although IR microspectrometry may suffer to some extent from the problems associated with the IR techniques described above such as the effect of adsorbed moisture, the spectra obtained by microspectrometry were found to have greater reproducibility in comparison with diffuse reflectance spectrometry. The principle disadvantage of microspectrometry is that IR spectra for individual particles or granules are obtained; thus the sample size is generally low. However, it was found that the IR spectra for different particles and duplicate spectra of an individual particle were reasonably reproducible. For these reasons, optical IR

microspectrometry was used to generate IR spectra of MCC particles.

An IR FT-spectrometer (Type 740, Nicolet Instruments Ltd., Warwick, U.K.) equipped with an IR plan microscope (Type cH, Spectra - Tek Ltd., Malton, Yorkshire, U.K.) was used to obtain transmission IR spectra for individual MCC particles. The spectra were recorded at a resolution of 8 cm^{-1} using 257 accumulated scans per sample type. In addition, subtraction spectra for Unimac MG-100 minus ungranulated Emcocel 50M, and for granulated minus ungranulated Emcocel 50M were generated using the associated equipment software to facilitate comparative analysis.

11.3.3.2 Attenuated total reflectance IR spectrometry

Attenuated total reflectance (ATR) IR spectroscopy, sometimes also known as internal reflectance spectroscopy, is a technique by which it is possible to characterise the surface layer of a sample to a depth of a few micrometers. The method has been described fully elsewhere (e.g. Colthup et al, 1975; Siesler & Holland-Moritz, 1980a). Briefly, the powder to be examined is pressed against a crystal / prism of a high refractive index. The IR beam is passed through the prism via a series of multiple reflections before reaching the detector. At each reflection at the sample / prism interface the vanishing or evanescent wave, which consists of the electrical field component of the incident wave, propagates a small distance into the sample. The exact distance of penetration is determined by the refractive indices of the sample and the prism, the wavelength of the IR radiation employed, and the actual angle of incidence at the sample / prism interface. The vanishing wave has a wavelength equal to that of the incident radiation but its amplitude decreases logarithmically with penetration depth. The evanescent wave is capable of interacting with an absorbing sample just beyond the interface and thus may be selectively attenuated in the wavelength regions at which the sample absorbs IR radiation. Multiple reflections are used to enhance the spectra of the radiation which emerges from the prism which is then passed to a detector. This technique is particularly useful for investigating samples which are optically dense.

An IR FT-spectrometer (Type 510, Nicolet Instruments Ltd., Warwick, U.K.) and a variable angle ATR cell (Model 300, Spectra - Tek Ltd, Malton, Yorkshire, U.K.) was used to obtain ATR spectra for individual MCC particles. The ATR was set up using a ZnSe prism with a refractive index of 2.4 and a

crystal face of 45°, and to provide an angle of incidence of 60°. This gave an approximate penetration depth of 2 μm at 2,000 cm^{-1} and 4 μm at 1,000 cm^{-1}. The spectra were recorded at a resolution of 4 cm^{-1} using 2,000 accumulated scans per sample type. In addition, subtraction spectra for Unimac MG-100 minus ungranulated Emcocel 50M, and for ungranulated minus granulated Emcocel 50M were generated using the associated data processing software to facilitate comparative sample analysis.

11.3.4 Solid state carbon-13 CP/MAS NMR spectroscopy

Spectra were obtained using a solid state carbon-13 nuclear magnetic resonance (^{13}C NMR) spectrometer (Type AC 300, Bruker Spectrospin Ltd., Coventry, U.K.) operating at approximately 75 MHz and equipped with a double air bearing magic angle spinning (MAS) probehead. In addition, the sample was spun at an angle of 54° 44', the 'magic angle', to the magnetic field. By averaging the chemical shift anisotropy of the molecules, MAS narrows bands and improves their resolution. Further, cross-polarisation (CP) was used to increase the sensitivity of the technique to ^{13}C nuclei, and was achieved using a contact time of 1 ms and a pulse sequence recycle delay of 3 seconds. Sample spinning speeds were typically 3,000 Hz. Chemical shifts were referenced to external adamantane. The software associated with the instrument enabled the subtraction spectra for Unimac minus ungranulated Emcocel 50M, and for ungranulated minus granulated Emcocel 50M to be obtained.

11.3.5 Moisture content

The moisture content after equilibration at a relative humidity of 53 % without severe sample pre-drying was determined using the method described in section 10.2.

11.4 Results

11.4.1 Effect of commercial source on the morphology of ungranulated MCC

11.4.1.1 Powder X-ray diffractometry

The powder X-ray diffractograms for ungranulated samples of various commercial forms and grades of MCC are shown in figure 11.2. For comparison, the diffractograms of highly crystalline samples of cellulose I and II, and for amorphous cellulose are shown in figure 11.1. (adapted from Nelson & O'Connor,

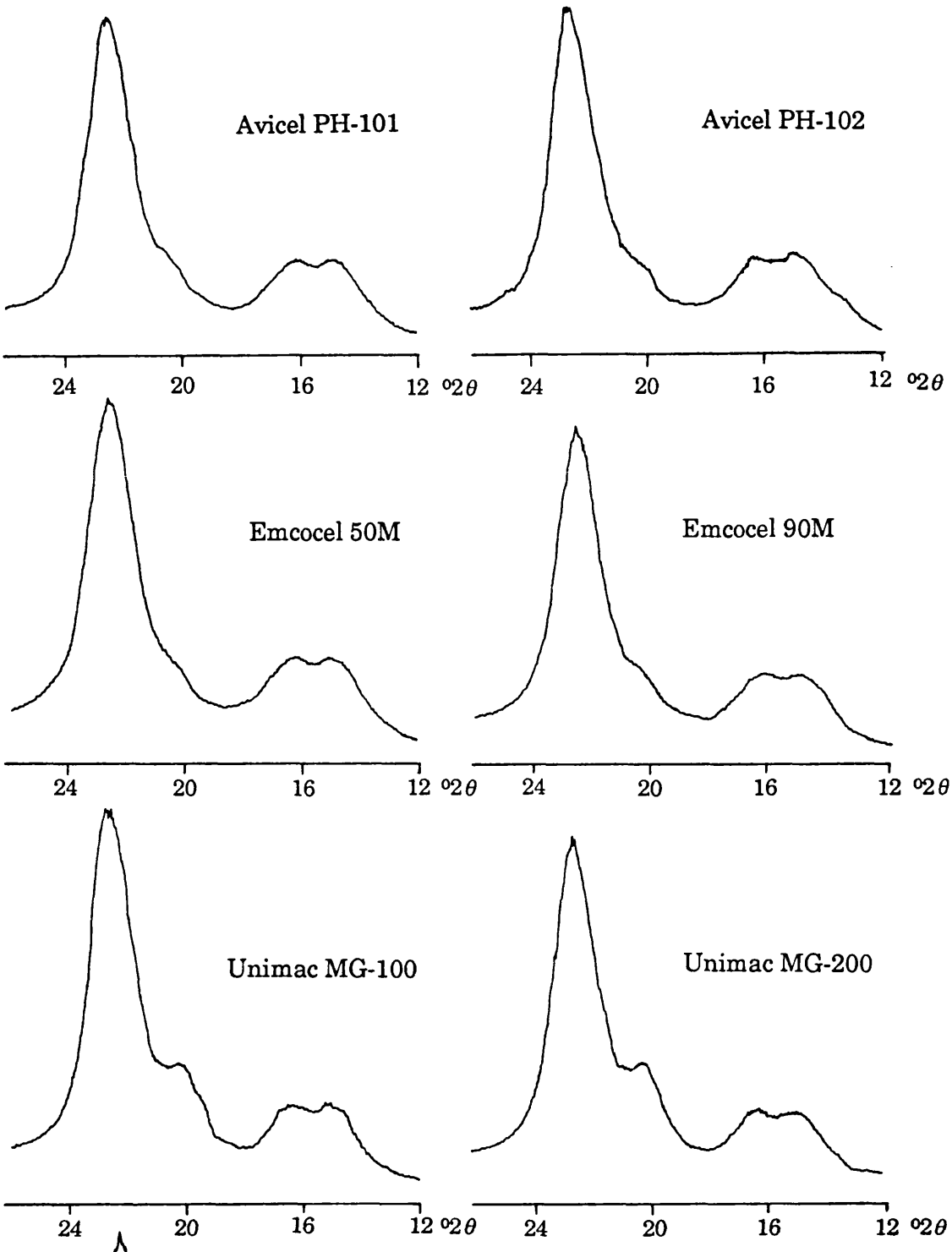


Figure 11.2 Powder X-ray diffractograms for MCC's from various commercial sources.

1964b). Differences in the lattice packing of molecular chains is responsible for differences between the diffractograms for different polytypes of cellulose. As a consequence of the relatively disordered chains producing largely random scattering of the X-ray radiation, amorphous cellulose gives rise to a diffuse halo.

The grades of Emcocel, Avicel, and Indocel investigated yielded similar diffractograms, (figure 11.2), indicating that the morphology of the cellulose in these commercial forms of MCC was similar. In addition, comparison with the spectra in figure 11.1 suggested that these MCCs principally comprised of cellulose I although there was some evidence of an additional amorphous phase. X-ray diffraction suffers from the disadvantage that for detection, the crystallites must be larger than a certain minimum size (Nelson & O'Connor, 1964b; Tripp, 1971). Thus, there may be minor differences in the morphology of the cellulose between these forms of MCC which are not readily apparent from their diffractograms.

The diffractograms for the two grades of Unimac clearly differed from those for the other sources of MCC, with the diffractograms for the Unimac materials exhibiting a shoulder centered at 20.5° 2θ (figure 11.2). Parker (1989) also reported that the X-ray diffraction spectra for Unimac MG-100 contained a shoulder which was not observed in the diffraction spectra for Avicel PH-101. However, in the study by Parker (1989), this shoulder was reported to occur at a diffraction angle of approximately 22° 2θ which is slightly higher than found for the shoulder in the present study. This discrepancy is perhaps related to differences between the spectrometers. However, Parker (1989) did not discuss reasons for the differences between the two commercial forms of MCC other than suggesting that the differences in the X-ray diffraction spectra reflected differences between the pre-treatment and manufacturing process of the two celluloses. Comparison with the diffractograms in figure 11.1 suggested that although predominantly cellulose I, the crystalline fraction of the Unimacs also consisted of some cellulose II. Comparison of the spectra of the two grades of Unimac material with spectra obtained by Ellefsen et al (1957) for physical mixtures of native and mercerised wood pulp suggests that of the crystalline fraction, approximately 20 to 30 % in Unimac MCCs may be attributable to polymorph II. However, as stated above, X-ray diffractometry is only sensitive to well ordered regions above a minimum size. Thus, this figure is only an estimate of the amount of cellulose II in Unimac MCCs. Unlike X-ray methods, IR, Raman

and solid state ^{13}C NMR spectroscopy are sensitive to the conformation and environment of individual molecules and so may yield further information regarding the relative proportions of cellulose I to II in Unimac MCCs. The results of such studies are discussed below.

Equation 3.1 provides a simple, if perhaps imprecise, method for estimating the relative degree of order between samples of cellulose. Although used by Nelson & O'Connor (1964b) to compare the crystallinity of samples of cellulose I and II and those containing mixed lattices, it has been proposed that the quantitative significance of crystallinity determinations based on X-ray diffraction is compromised when applied to mixed lattices (Wadsworth & Cuculo, 1978). With this limitation in mind, the percentage of crystalline material in each form of MCC investigated was determined. The results are presented in table 11.2 and reveal that the commercial forms of MCC investigated contained similar proportions of highly ordered and thus also disordered (amorphous) material. This is in contrast to the results of Doelker et al (1987b) in which wide differences were reported between the crystallinity of various commercial forms of MCC as determined by X-ray diffractometry. In the study by Doelker et al (1987b) values for crystallinity were calculated using a different mathematical analysis method to that used in the present study. It is possible that differences between the accuracy of the methods used to calculate the degree of crystallinity or inter batch variations between the samples used by Doelker et al (1987b) and those used in the present study may account for the discrepancy between the two sets of results.

Table 11.2 Percentage of crystalline material in various commercial forms and grades of MCC

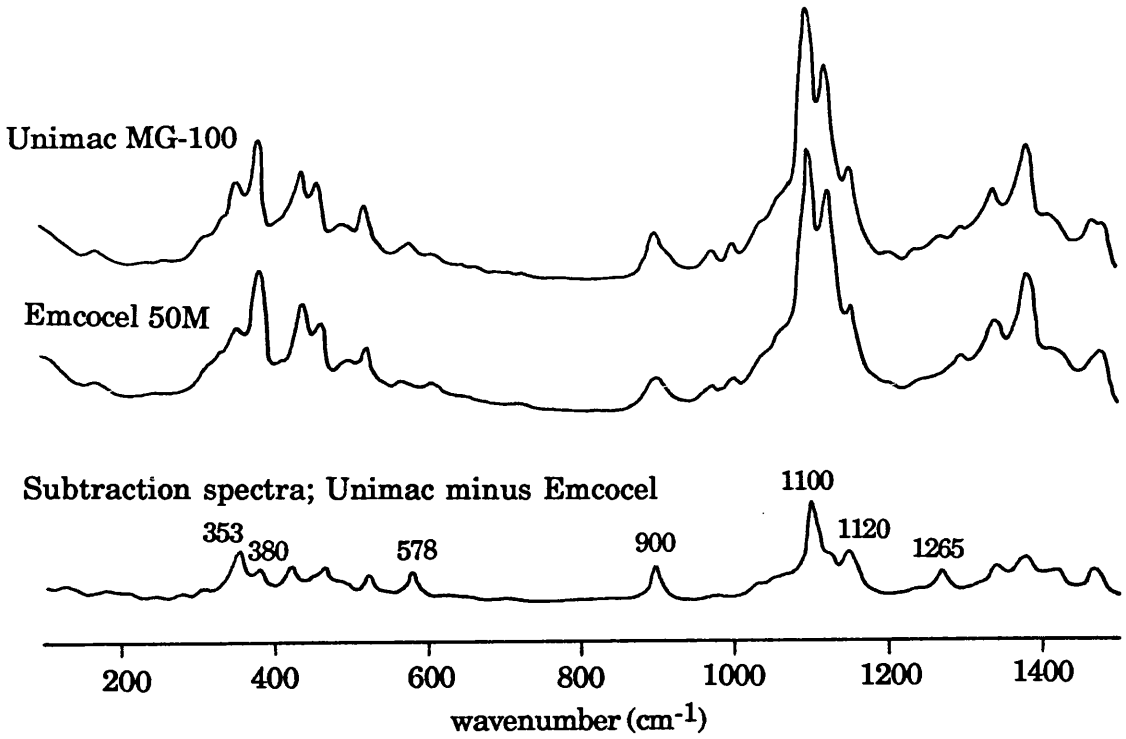
Commercial form and grade of MCC	Percentage crystalline material (*%Cr*)
Avicel PH-101	86%
Avicel PH-102	87%
Emcocel 50M	87%
Emcocel 90M	85%
Unimac MG-100	86%
Unimac MG-200	86%
Indocel 80	86%

11.4.1.2 Raman spectrometry

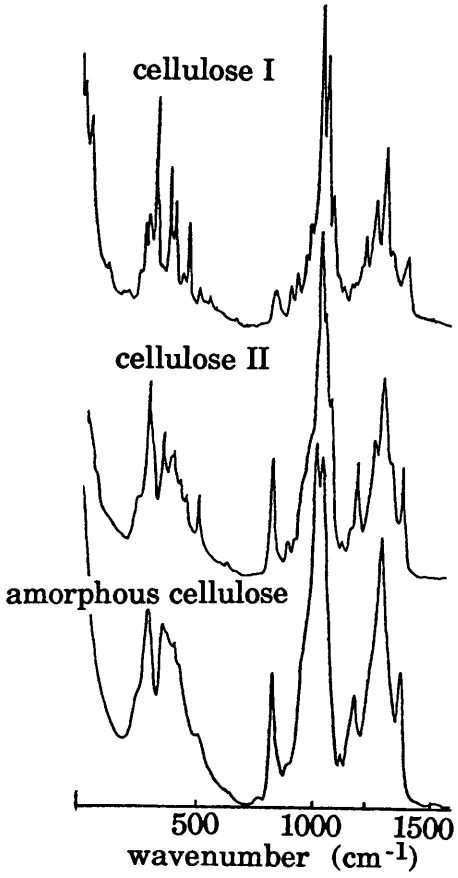
Raman spectrometry is similar to IR spectrometry in that both techniques involve investigation of molecular vibrations. However, in order to absorb IR radiation, a molecular vibration must cause a change in the dipole moment of the molecule. In contrast, the molecular vibration must possess anisotropic polarisability to produce Raman spectra. Thus, bonds which are highly polar such as O-H bonds in cellulose and water tend to absorb electromagnetic energy strongly in the infrared region, whereas bonds primarily covalent in character such as skeletal and C-H bonds generally absorb poorly in the infrared region but result in intense bands in Raman spectra. In addition, in Raman spectroscopy the radiation detected is that which is scattered by the sample. As a result, optical effects and moisture adsorption generally do not present problems in interpretation of Raman spectra, although both phenomena cause artefacts in IR spectroscopy.

Spectra for ungranulated Emcocel 50M and Unimac MG-100 obtained using Raman spectrometry together with the subtraction spectra for Unimac minus Emcocel are shown in figure 11.3a. The three spectra were reproduced at least once and did not show inconsistencies. For comparison, Raman spectra obtained by Atalla (1983) for samples of highly crystalline cellulose I and II and for amorphous cellulose are shown in figure 11.3b. The small scale for wavenumber used in the latter spectra present difficulties when attempting to compare the spectra obtained by Atalla (1983) with those obtained in the present study. Thus, additional spectra also obtained by Atalla (1981) for highly crystalline cellulose I and II are also shown in figure 11.3c. Band assignments and models for the structures of cellulose have been reported by Atalla (1976). Differences between cellulose I and II were attributed to differences in the molecular conformation of chains between the two polymorphs rather than differences solely due to the packing and hydrogen bonding patterns between the two forms. However, although the Raman spectra for cellulose I and II contain distinct differences, the spectra for cellulose II is similar to that for amorphous cellulose.

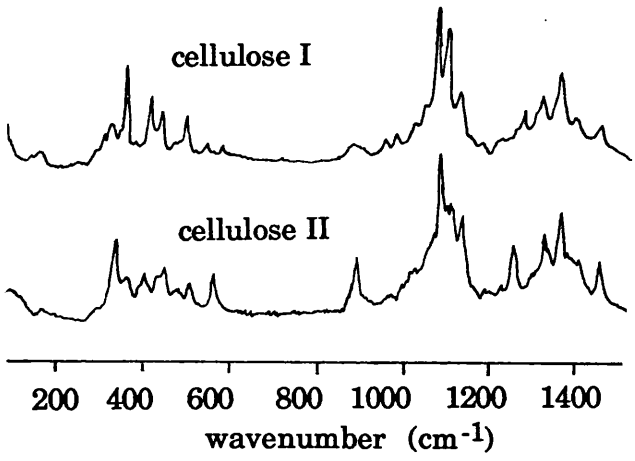
The spectra for Unimac and Emcocel appear similar and comparable with that of highly crystalline cellulose I obtained by Atalla (1976, 1983). However, the subtraction spectrum contains relatively intense absorptions at 578, 900 and 1265 cm^{-1}, and the peak at 353 cm^{-1} has a higher intensity than that at 380 cm^{-1} (figure 11.3a). These features, together with the relative intensities of the peaks at



a. Raman spectra for Unimac MG-100 and Emcocel 50M, together with the subtraction spectra for Unimac minus Emcocel.



b. Raman spectra for standard cellulose samples, adapted from Atalla (1983).



c. Raman spectra for standard cellulose samples, adapted from Atalla (1981).

Figure 11.3 Raman spectra for Unimac MG-100 and Emcocel 50M, and for standard samples of cellulose I and II and amorphous cellulose.

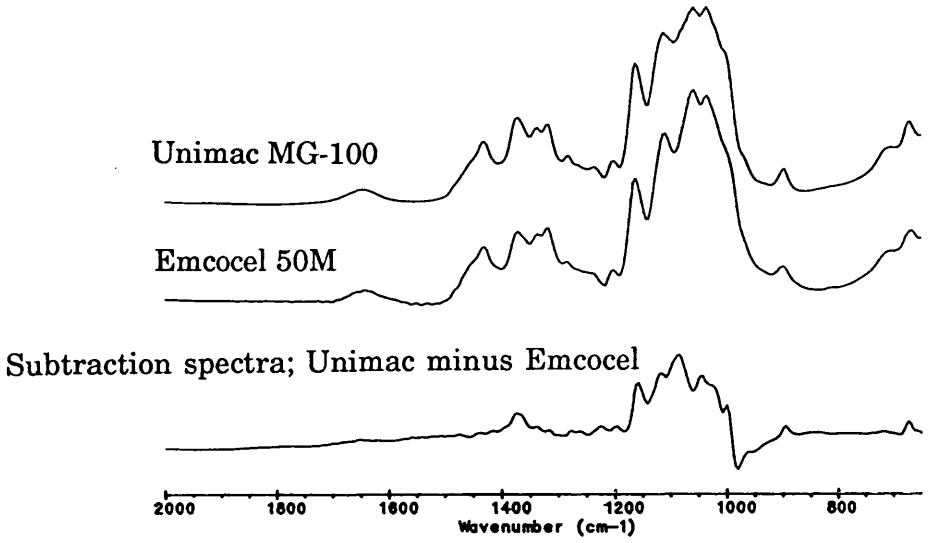
1100 and at 1120 cm^{-1} in the subtraction spectrum, suggest the presence of additional cellulose II and / or amorphous cellulose in Unimac. Further, the presence of distinct peaks between 300 and 600 cm^{-1} in the subtraction spectra suggests that the subtraction spectra is more likely due to additional cellulose II rather than additional amorphous cellulose.

11.4.1.3 IR spectrometry

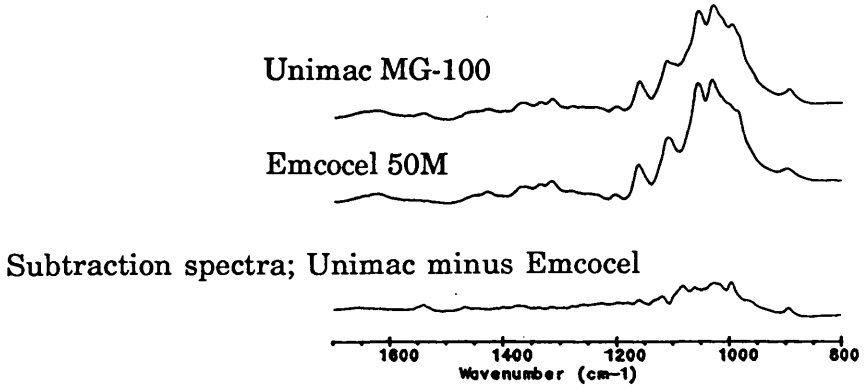
The IR spectra obtained from optical microspectrometry for bulk particles of ungranulated Emcocel 50M and Unimac MG-100, together with the subtraction spectra for Unimac minus Emcocel are shown in figure 11.4a. The ATR IR spectra for Unimac, Emcocel, and Unimac minus Emcocel are shown in figure 11.4b. All spectra were reproduced at least once showing no inconsistencies. For comparison, infrared spectra for highly crystalline cellulose I and II, and for amorphous cellulose (adapted from Nelson & O'Connor, 1964a), are shown in figure 11.4c.

Band assignment and differences between the IR spectra of polymorphs I and II have been discussed elsewhere (Nelson & O'Connor, 1964a; Blackwell, 1971 and 1977). Nelson & O'Connor (1964a) noted that cellulose II and amorphous cellulose yielded similar IR spectra, both differing slightly from cellulose I at certain frequencies. The principle changes in the IR spectra on conversion of cellulose I to cellulose II were reported to be a decline in the intensity of the bands at 1430 and 1162 cm^{-1}, and an increase in the intensity of the band at 895 cm^{-1} (Nelson & O'Connor, 1964a; Blackwell, 1971 and 1977). Changes in the intensity of these bands has been used to follow the mercerisation process for a variety of celluloses, although the similarities between the spectra for cellulose II and amorphous cellulose limits the use of IR spectra for quantifying the relative proportions of polymorphs I and II (Blackwell, 1971).

Considering the bulk particle spectra for Unimac and Emcocel (figure 11.4a), superficially there appears to be little difference between the two MCCs. However, the subtraction spectra contains peaks at 895 and 1370 cm^{-1} which on comparison with the spectra in 11.4c obtained by Nelson & O'Connor (1964a) suggests the presence of additional cellulose II in the Unimac sample. It should, however, be noted that the peaks between 1000 and 1200 cm^{-1} in the subtraction spectra may have arisen from mis-calculation, an artifact sometimes encountered



a. Infra red spectra for Unimac MG-100 and Emcocel 50M, together with the subtraction spectra for Unimac minus Emcocel obtained using optical infra red microspectrometry.



b. Infra red spectra for Unimac MG-100 and Emcocel 50M, together with the subtraction spectra for Unimac minus Emcocel obtained using attenuated total reflectance spectrometry.

c. Infra red spectra for standard cellulose samples, adapted from Nelson & O'Connor (1964a).

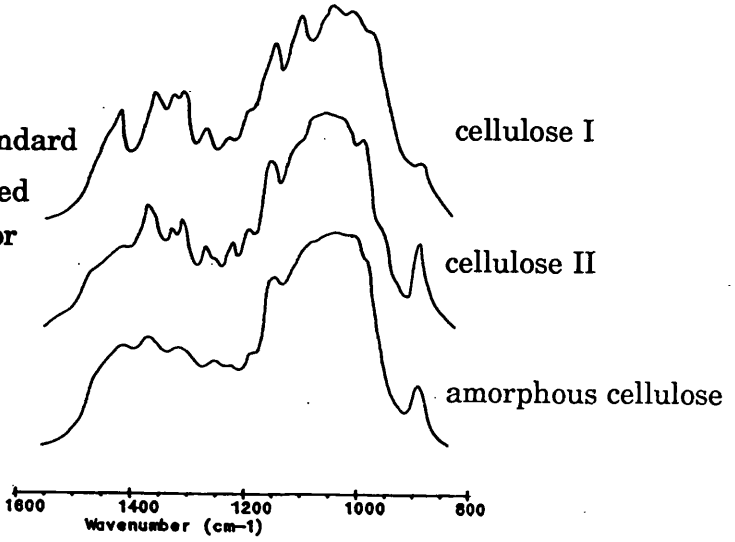


Figure 11.4 Infra red spectra for Unimac MG-100 and Emcocel 50M, and for standard samples of cellulose I and II and amorphous cellulose.

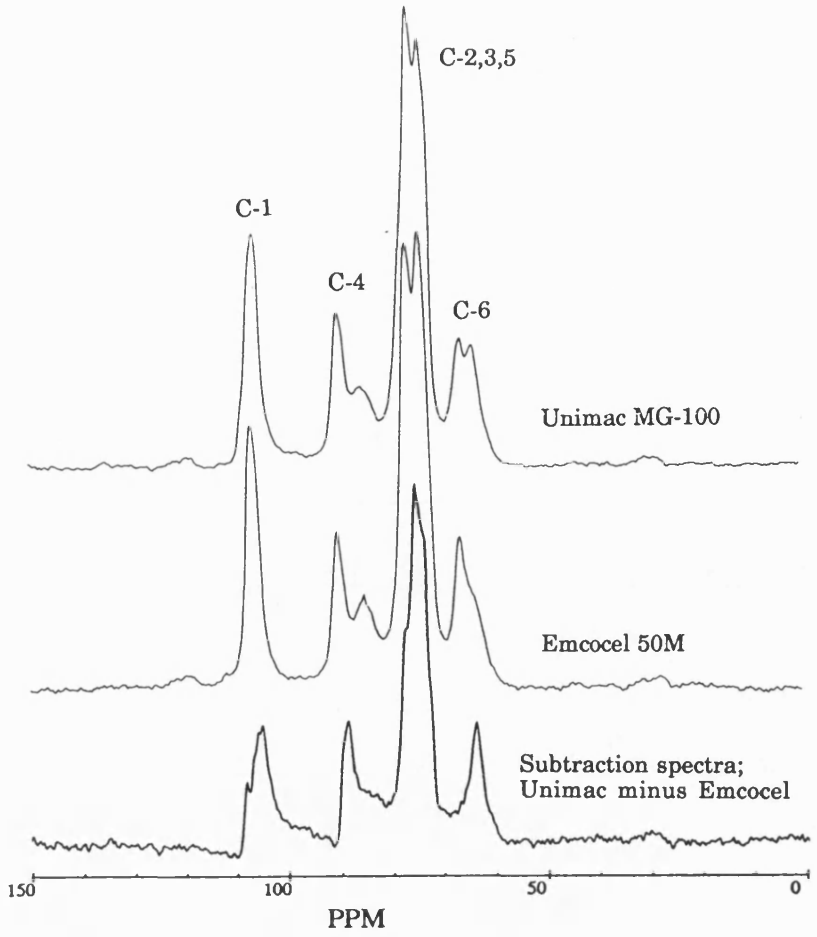
during subtraction of peaks with high intensity (Luk, 1991).

The general form of the ATR spectra (figure 11.4b) was similar to spectra obtained using optical microspectrometry (figure 11.4a). Further, due to the shallow penetration depth of the ATR beam, there was relatively low absorbtion and so subtraction was achieved with greater success, particularly between 1000 and 1200 cm^{-1}, in comparison with optical microspectrometry. Although a relatively distinct peak at 895 cm^{-1} was observed in the subtraction spectra, unlike in the subtraction spectra obtained using optical IR microspectrometry, a distinct peak at 1370 cm^{-1} was absent in the ATR subtraction spectra. The anomolous band at 1550 cm^{-1} was suspected to be an artefact or impurity on the ZnSe crystal and for this reason was ignored. Because of difficulties in interpretation of the spectra, IR spectroscopy was not found useful in comparison with X-ray diffractometry and Raman spectroscopy for examining small differences in polymorphic form of cellulose samples. More interesting, however, was the broad similarity between the IR spectra obtained by optical microspectrometry and ATR which suggested that the polymorphic composition of the particle bulk was similar to that of the surface layer up to 2-4 μm in depth.

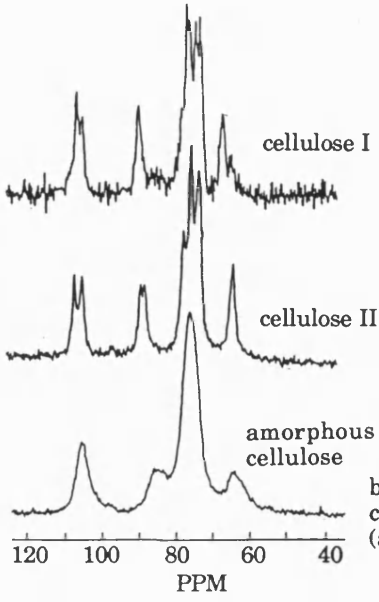
11.4.1.4 Solid state CP/MAS ^{13}C NMR spectroscopy

^{13}C NMR spectroscopy reveals information regarding the solid-state environment of the carbon atoms. Chemical shift differences for a given carbon site can be interpreted as indicating the presence of cellulose molecules with differing bond angles or undergoing different degrees of bonding (Earl & Vanderhart, 1980). The ^{13}C NMR spectra for ungranulated Emcocel 50M and Unimac MG-100 are shown in figure 11.5a. For comparative purposes, the spectra for highly crystalline polymorphic forms I and II, together with the spectra for completely amorphous cellulose obtained by Atalla et al (1980) are shown in figure 11.5b. Annotations regarding the assignment of resonance peaks to specific carbon atoms in the cellulose molecule in figure 11.5a for cellulose I are in accordance with the convention shown in figure 1.1.

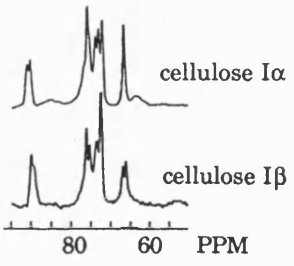
Comparison of the form of the C-4 resonance (at approximately 88 ppm) for both Emcocel and Unimac (figure 11.5a) with the spectra for standards (figure 11.5b) indicate that both commercial forms are moderately to highly crystalline but contain some amorphous material. Emcocel and Unimac differ with respect to



a. ^{13}C-NMR spectra for Unimac MG-100 and Emcocel 50M, together with the subtraction spectra for Unimac minus Emcocel.



b. ^{13}C-NMR spectra for standard cellulose I, II and amorphous cellulose (adapted from Atalla et al; 1980)



c. ^{13}C-NMR spectra for standard cellulose Iα and Iβ (adapted from Vanderhart & Atalla; 1984)

Figure 11.5 ^{13}C-NMR spectra for Unimac MG-100 and Emcocel 50M, and for standard samples of cellulose I, II, Iα,Iβ, and amorphous cellulose.

the form of the C-6 resonance (at approximately 65 ppm). In the case of Emcocel the C-6 resonance yields a peak at approximately 67 ppm, suggesting cellulose I, with a broad shoulder centred around approximately 64 ppm, which may be due to the presence of amorphous cellulose. By comparison, Unimac yields peaks at 67 ppm and 64 ppm. The form of the peak at 64 ppm, although occurring at a similar chemical shift as the broad resonance associated with C-6 in amorphous cellulose, suggests that this additional peak is not solely attributable to the presence of additional amorphous cellulose, but is a consequence of cellulose II. The subtraction spectrum for Unimac minus Emcocel (figure 11.5a) confirms the presence of an additional sharp peak as opposed to a broad resonance at approximately 64 ppm in the Unimac spectra. It should also be noted that the resonance for C-6 in cellulose II has a lower chemical shift than for either cellulose Iα or Iβ (figure 1.5c, adapted from Vanderhart & Atalla, 1984). Hence the additional peak at approximately 64 ppm in the spectra for Unimac is unlikely to be due to differences in the ratio of cellulose Iα and Iβ between the two samples. Unfortunately, the comparatively poor resolution of the resonances corresponding to carbons 2, 3 and 5 in the spectra for the two MCC's occludes additional conclusive evidence regarding differences in morphology between Unimac and Emcocel, although the general shape of these resonances in the subtraction spectrum is consistent with cellulose II. It should also be noted that the C-1 and C-4 resonances in the subtraction spectrum appear distorted when compared with those in the spectra for cellulose II obtained by Atalla et al (1980). The distortions possibly arise from differences in the ratios of cellulose Iα and Iβ and amorphous cellulose between the two commercial forms.

11.4.1.5 Moisture content

The equilibrium moisture contents are presented in this part of the study since they are related to the degree of crystallinity and polymorphic form of cellulose. The moisture contents for the grades of Emcocel, Avicel and Unimac investigated following equilibration at a relative humidity of approximately 53 % are presented in table 11.3.

From table 11.3 it can be seen that there is little if any difference between the moisture absorbing abilities between the MCCs investigated. Bassam et al (1988) and Parker (1989) reported that Unimac materials attain a lower

Table 11.3 The equilibrium moisture content of various commercial forms of MCC (95% confidence interval given in parenthesis)

Commercial form	Equilibrium moisture content (%)
Emcocel 50M	6.05 (± 0.04)
Emcocel 90M	5.97 (± 0.05)
Avicel PH-101	6.00 (± 0.04)
Avicel PH-102	6.04 (± 0.02)
Unimac MG-100	5.95 (± 0.05)
Unimac MG-200	5.98 (± 0.02)

equilibrium moisture content than Avicel materials following storage under similar conditions. However, a substantial difference between the moisture content of these two commercial forms was not found in the present study, perhaps due to inter-batch differences.

11.4.1.6 Discussion

As discussed in section 1.5.1, differences between the tableting performance of various commercial forms of MCC have been reported by other workers. For example, grades of Unimac have been reported to exhibit inferior compactibility in comparison with equivalent particle size grades of Avicel and Emcocel (Doelker et al, 1987a; Whiteman & Yarwood, 1988), the three commercial forms also differing with respect to their Young's moduli (Bassam et al, 1988) and wet massing characteristics (Rowe & Sadeghnejad, 1987; Parker et al, 1988). Further, it has been suggested that the surface energetics of Avicel PH-101 and Unimac MG-100 differ from each other (Parker et al, 1988; Parker, 1989). It is commonly considered that differences such as those described immediately above arise from differences between the method of manufacture of various commercial forms. However, more specific physico-chemical reasons for these differences are incompletely resolved. Although the degree of crystallinity of MCC samples from various sources may differ (Doelker et al, 1987b), such variations have not been found to correlate with differences between compaction characteristics (Doelker et al, 1987c). However, the question of variation in

polymorphic form between commercial forms of the excipient and its influence on tableting characteristics has hitherto been ignored.

In the present study Emcocel 50M and 90M, Avicel PH-101 and PH-102 and Indocel 80 were found to exhibit similar powder X-ray diffractograms indicating similar morphologies for the cellulose in these three commercial forms which was also characteristic of cellulose I with a minor amorphous phase. Spectroscopic techniques confirmed that Emcocel 50M, and by inference Emcocel 90M and the Avicels and Indocel, were all composed of moderately to highly crystalline cellulose I. X-ray diffractometry, and Raman and solid state CP/MAS ^{13}C NMR spectroscopy indicated that although predominantly composed of cellulose I, Unimac MG-100 contained an additional cellulose II phase. ^{13}C NMR spectroscopy also suggested that the ratios of $I\alpha$ to $I\beta$ as well as the ratios of crystalline to amorphous cellulose may differ between Emcocel 50M and Unimac MG-100. The similarity of the X-ray diffractograms for the two grades of Unimac suggested that Unimac MG-200 also contained cellulose II in addition to cellulose I and amorphous cellulose. In both grades of Unimac, cellulose II was estimated to account for approximately 20 - 30% of the crystalline fraction. The degree of crystallinity indicated by diffractometry for all of the commercial forms of MCC studied was found to be similar, being approximately 66 - 67 %. Powder X-ray diffractometry and Raman and ^{13}C NMR spectroscopy were found to be the techniques of choice for examining the polymorphic form of MCC.

The differences in polymorphic form between commercial forms of the excipient may be a consequence of differences in the manufacturing process. For example, the production of Unimac may involve the use of a swelling agent such as sodium hydroxide resulting in some conversion of cellulose I to cellulose II (section 1.3.1.3) . Alternatively, the production of all three forms of MCC may involve the use of potential chemical swelling agents, but differences in the biological source of the starting cellulose may result in differing degrees of conversion to cellulose II. Differences in the starting material are likely and would also account for possible differences in the ratios of cellulose $I\alpha$ and $I\beta$ in Emcocel 50M and Unimac MG-100 as indicated by ^{13}C NMR spectroscopy.

When considering the consequence of the effect of polymorphic form on the physico-mechanical properties of MCC, it may be considered useful to consider parallels between MCC and cellulose. However, mercerisation of

unhydrolysed cellulose has been found to reduce its degree of crystallinity (Jeffries, 1968; Cabradilla & Zeronian, 1978). Thus, any changes observed in the physico-mechanical properties of cellulose fibres resulting from mercerisation probably result from differences in the amount of crystalline material rather than from differences in lattice structure between cellulose I and II (Nicoll et al, 1983). Further, it is considered likely that lower compactibility of Unimacs in comparison with Avicels and Emcocels are due to the differences between the deformation characteristics of spray dried aggregates rather than differences between individual microcrystal deformability. However, it is further possible that the presence of cellulose II in Unimacs may result in different bonding characteristics in comparison with microcrystals composed solely of cellulose I, thus perhaps partially accounting for differences between the physico-chemical characteristics of Unimacs and other MCCs reported elsewhere.

It has also been suggested that cellulose II may absorb moisture within microcrystals whereas microcrystals of cellulose I apparently do not exhibit such behaviour (Hermans & Weidinger, 1949). However, the conclusions drawn in the latter study have been criticised by Howsmon & Sisson (1954) who suggested that conclusive evidence as to whether this effect was due to alteration in polymorphic form rather than a reduction in the degree of order within the structure following conversion to cellulose II was lacking. An increase in the MCC equilibrium moisture content may improve compactibility (section 1.5.4.5). However, in the present study the presence of cellulose II in Unimac samples was not reflected in increased moisture content in comparison with other commercial forms of MCC. Thus, the present results suggest that the presence of cellulose II in Unimac does not directly influence the physico-mechanical characteristics of MCC through its possible effect on the equilibrium moisture content.

Direct investigation of the effect of polymorphic form on the compactibility of MCC would be of interest. Preparation of microcrystalline samples consisting of cellulose with varying proportions of cellulose I and II but comparable in all other respects would be problematic, however, since conversion of polymorph I to II is likely to reduce the crystallinity and thus also reduce the degree of polymerisation of microcrystalline samples (Cabradilla & Zeronian, 1978). These factors may be expected to increase the moisture content, thus complicating interpretation of the results which would be obtained.

11.4.2 Effect of wet granulation on the polymorphic form and degree of crystallinity of MCC

11.4.2.1 Powder X-ray diffractometry

Powder X-ray diffractograms for ungranulated and wet granulated and dried Emcocel 50M are shown in figure 11.6. The diffractograms appear similar in form, and by comparison with the diffractograms presented in figure 11.1. suggest that wet granulation does not result in an alteration in the polymorphic form of the crystalline component of the cellulose which is apparently cellulose I. However, as discussed in section 11.4.1.1 above, this technique does not assess the conformation of individual chains on a molecular level. Hence the diffractograms do not preclude the presence of, for example, small amounts of cellulose II on the surface of the particles.

The degrees of crystallinity obtained from analysis of powder X-ray diffractograms were found to be 87 % for ungranulated and 86 % for granulated MCC, indicating no significant change in the degree of order as determined by this technique following wet granulation.

11.4.2.2 Raman spectroscopy

The Raman spectra for ungranulated and wet granulated MCC together with the subtraction spectra for granulated minus ungranulated Emcocel 50M are shown in figure 11.7. From the subtraction spectra it does not appear that wet granulation caused a change in the morphology of the cellulose. In addition, the similar nature of the spectra indicates that granulation does not alter the molecular chain conformation, for example through quasi-hornification.

11.4.2.3 Infrared spectroscopy

The IR spectra for bulk particles for ungranulated and wet granulated MCC, and the subtraction spectrum for granulated minus ungranulated Emcocel 50M obtained by optical microspectrometry are shown in figure 11.8a. The absorptions in the subtraction spectra in the region 1000 to 1200 cm^{-1} are likely to have arisen from mis-cancelation of intense absorbances and thus were considered inappropriate for assessing alteration in the form of cellulose by wet granulation. The ATR spectra for ungranulated and granulated Emcocel 50M are shown in figure 11.8b together with the subtraction spectra for granulated minus

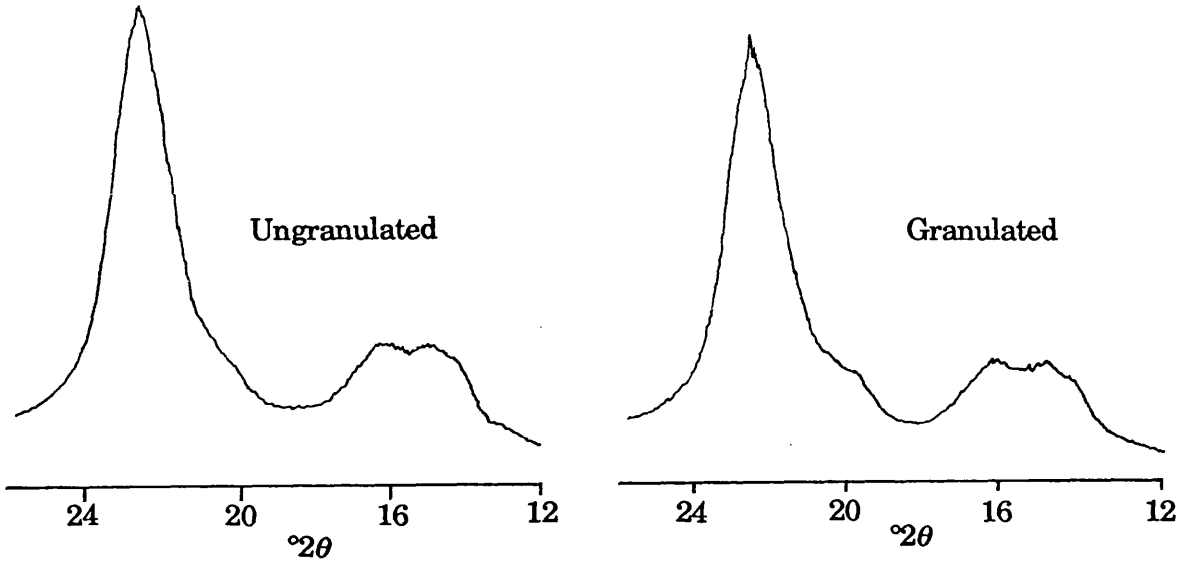


Figure 11.6 Powder X-ray diffractograms for ungranulated and granulated Emcocel 50M.

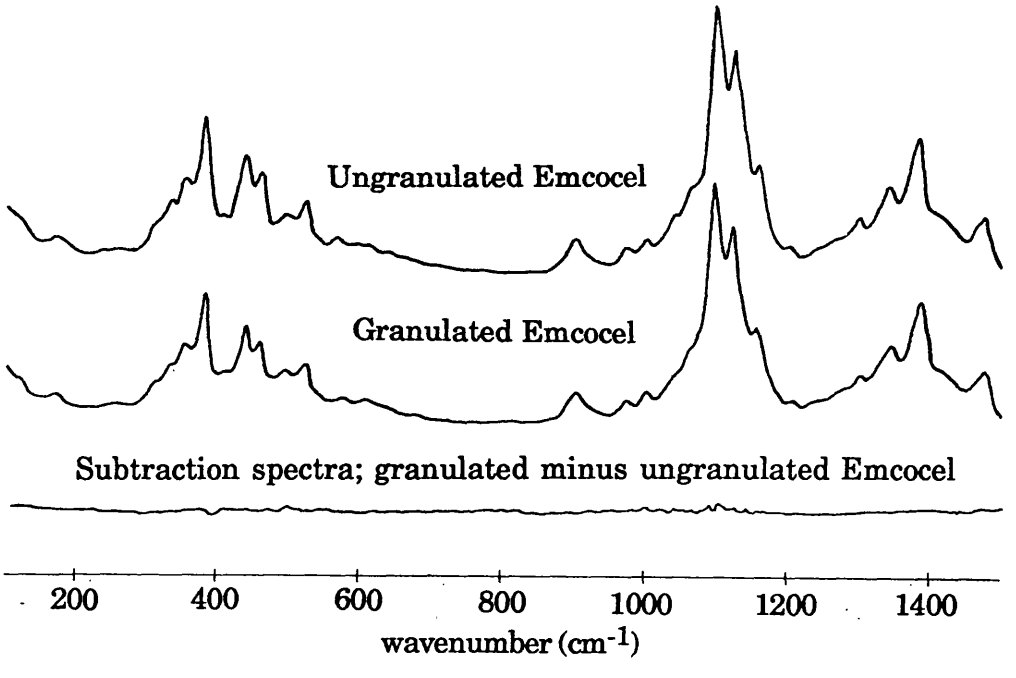
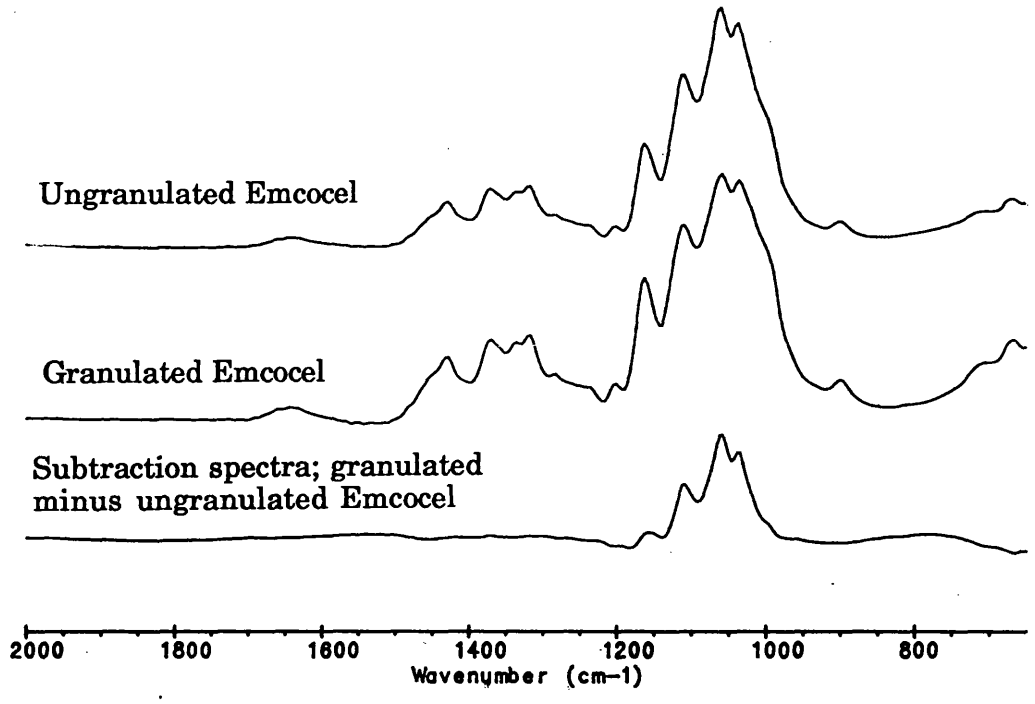
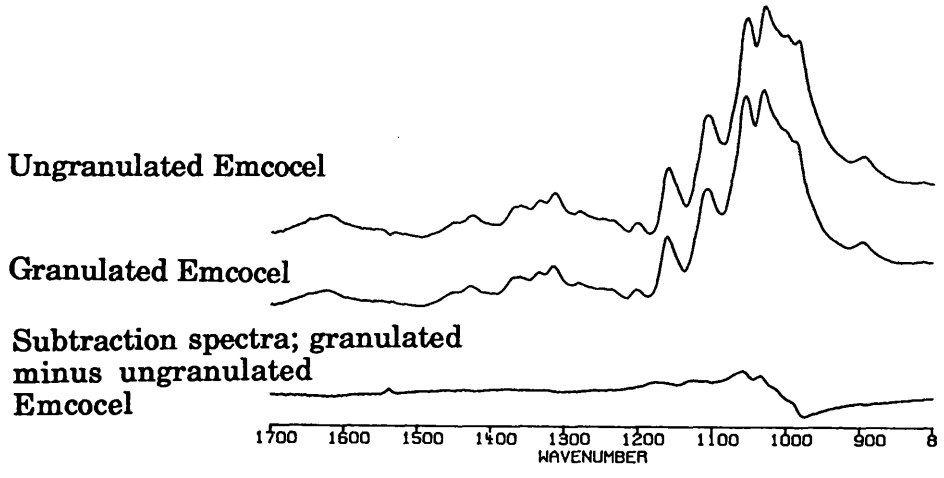


Figure 11.7 Raman spectra for ungranulated and granulated Emcocel 50M, together with the subtraction spectra for granulated minus ungranulated Emcocel.



a. Optical microspectra



b. Attenuated total reflectance spectra

Figure 11.8 Infra red spectra for ungranulated and granulated Emcocel 50M, together with the subtraction spectra for granulated minus ungranulated Emcocel.

ungranulated Emcocel. The subtraction spectrum was not flat, and initially it was considered that the deviations of the subtraction spectra from a flat line was artifactual, perhaps due to differences between the sample presentation. However, although not shown here, replicate analyses using fresh samples of the same type yielded a similar subtraction spectra to that shown in figure 11.8b. Further, subsequent studies using regenerated cellulose fibres which were considered to vary in the amount of bonding, but which are outside the scope of the present study, have been found to give consistently similar subtraction spectra when the less 'crystalline' fibre is subtracted from the more 'crystalline' fibre (not shown here) to the subtraction spectra shown in figure 11.8b. Thus the subtraction spectra in figure 11.8b may be real and associated with phenomena occurring as a result of cellulose processing. Research in this area is still proceeding. However, preliminary results suggest that granulation may result in an increase in the amount of hydrogen bonding within MCC particles which is consistent with the theory presented in section 3.4.1 that granulation causes quasi-hornification of MCC and further, ATR may be useful technique for directly investigating the phenomenon of quasi-hornification.

11.4.2.4 Solid state 13C NMR spectroscopy

The ^{13}C NMR spectra of ungranulated and granulated Emcocel (figure 11.9) revealed that the cellulose in the two samples was of near-identical morphology. Thus, possible increased hydrogen bonding levels within MCC particles following wet granulation due to the phenomenon of quasi-hornification were not apparent from NMR spectra.

11.4.2.5 Discussion

Physical processes involving intense mechanical agitation such as ball milling are well known to reduce the degree of crystallinity of cellulose (e.g. Nelson & O'Connor et al, 1964b; Nakai et al, 1977a). Further, it has been reported that the rate of decrystallisation arising from mechanical agitation is accelerated in the presence of atmospheric moisture (Howsmon & Marchessault, 1959). X-ray diffraction studies have also indicated that in the presence of liquid water or water vapour, a proportion of the resulting amorphous material may recrystallise as cellulose I provided that over 25 % of the sample remains as cellulose I after milling (Howsmon & Marchessault, 1959; Bhama et al, 1984).

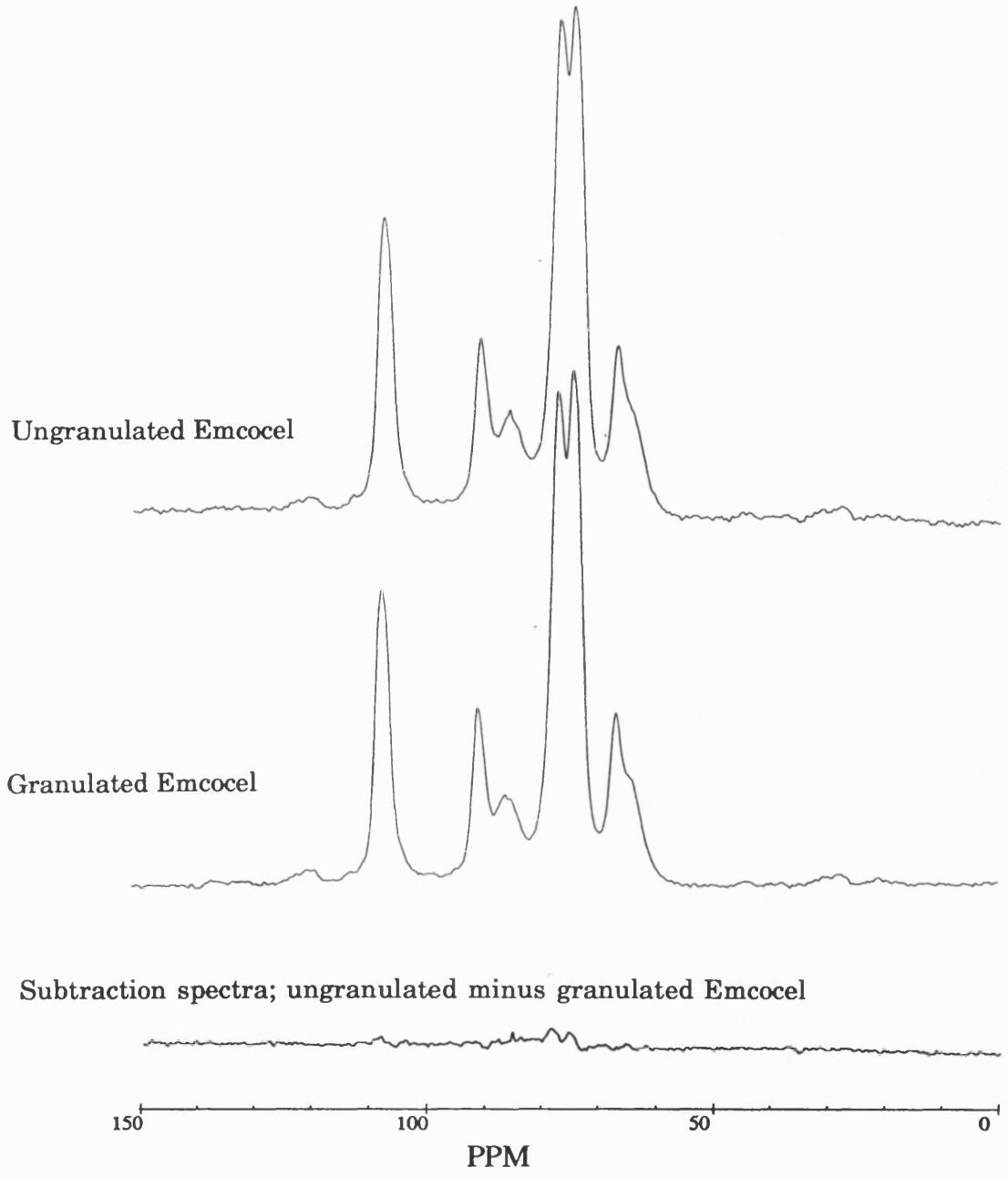


Figure 11.9 ^{13}C-NMR spectra for ungranulated and granulated Emcocel 50M together with the subtraction spectra for ungranulated minus granulated Emcocel.

However, if the amorphous content in milled samples exceeds 75 %, amorphous cellulose may partially recrystallise as polymorph II (Howsmon & Marchessault, 1959; Nelson O'Connor, 1964a, Bhama et al, 1984). Using Raman spectroscopic analyses, Atalla also reported that a small proportion of cellulose I was converted to cellulose II either as a result of wet refining (Atalla, 1981), or from mechanical treatment of cellulose in the presence of water (Atalla, 1983). The mechanism of transformation was suggested to involve solvation or swelling of some of the cellulose on a molecular level (Atalla, 1981). Upon drying, cellulose chains in the 'swollen' regions adopted the molecular conformation associated with cellulose II rather than cellulose I as less molecular strain is associated with polymorph II in comparison with polymorph I (Atalla, 1983). Although wet granulation of MCC involves intense agitation in the presence of water, the results obtained in the present study indicate that granulation does not result in a significant alteration in the degree of crystallinity or polymorphic form of MCC. It is therefore reasonable to conclude that neither phenomena contribute to the loss in compactibility of MCC following wet granulation.

IR spectroscopy is a potentially useful technique for assessing the relative amounts of hydrogen bonding contained within different cellulose samples because O-H vibrations absorb IR radiation strongly. Over the wavenumber ranges investigated in the present study an increase in hydrogen bonding could be expected to increase the wavenumber for absorptions associated with the O-H in-plane deformation which are the absorptions occurring between 1000 and 1650 cm^{-1} (Siesler & Holland-Moritz, 1980b). However, an increase in the degree of hydrogen bonding which might have indicated hornification following wet granulation was not readily observed using IR spectroscopy, although its occurrence cannot be discounted because of the problem of mis-cancelation of spectra which may have concealed such shifts. In addition, when discussing the possibility of observing increased hydrogen bonding such as considered to occur during papermaking from wood pulp fibres, Higgins & De Yong (1962) suggested that IR spectroscopy was unlikely to reveal differences between unprocessed fibres and those bonded together since the number of hydrogen bonds in unprocessed fibres was very high and bonding arising from papermaking would be expected to increase this by only a small, perhaps undetectable, fraction. IR spectra in the range 3400 to 3200 cm^{-1} may yield further information regarding the increased hydrogen bonding between samples. In this range the wavenumber

associated with O-H stretching would be expected to decrease and the intensity of the band to increase with increased hydrogen bonding (Siesler & Holland-Moritz, 1980b). However, the presence of adsorbed water may complicate interpretation of spectra at these frequencies. In the present study, the occurrence of hornification, or increased hydrogen bonding within particles following wet granulation of MCC was not conclusively detectable by spectroscopic techniques in the wavenumber and chemical shift ranges investigated. However, ATR studies indicated that its occurrence could not be discounted.

Chapter 12. A study of the effect of additive substances on the compaction properties of MCC granules

12.1 Objectives and background

Work reported above suggested that increased intraparticle hydrogen bonding due to a phenomenon termed quasi-hornification (section 3.4.1 et seq.) was a significant contributor to reducing the compactibility of MCC following wet granulation. It was therefore hypothesised that by reducting in intermolecular hydrogen bonding occurring as a result of wet granulation of MCC, quasi-hornification could be reduced or eliminated and its compactibility thereby improved.

Other workers have proposed methods by which cellulose - cellulose hydrogen bond formation during drying of water-wet cellulose may be reduced (section 1.4.3). Three possible mechanisms were considered in the present investigation by which hydrogen bonding, and therefore intraparticle bonding, could be reduced during aqueous granulation in order to improve granule compactibility: Firstly, inclusion of a surface active agent in the granulation fluid to reduce the surface tension of the granulation fluid in order to reduce intraparticle collapse during drying; secondly, addition to the wet granules before drying a material which would reduce intermicrocrystal bonding by its physical presence or by physically swelling intragranular surfaces, and thirdly, addition of a material to the granulation fluid which could adsorb and bond to cellulose microcrystals, inhibiting the formation of inter-microcrystal cellulose - cellulose hydrogen bonds. A required characteristic of this third additive type was that on compaction, unlike cellulose - cellulose bonds, the additive - cellulose bond would have a sufficiently low mechanical strength to allow a high degree of granule deformation.

It was considered that many of the conventional techniques by which the degree of hornification could be assessed (described in section 1.4.4) were either too complex, for example the solute exclusion technique described by Stone & Scallen (1968), or inappropriate for examining quasi-hornification of MCC, for example measurement of the collapse of the fibre lumen as a result of drying (Page, 1967). Additional physico-chemical characterisation techniques for semi-quantification of the extent of quasi-hornification occurring as a result of wet

granulation of MCC described in previous parts of the present study such as determination of MCC specific surface area or bulk density were also found to have their limitations. For this reason, the effect of additives on wet granulated MCC was assessed by investigating the compactibilities of treated granules. This also provided a more appropriate test for the effect of the additives on the granule properties in the use for which they are intended. Work reported elsewhere in the present study indicated that for comparison, granules should be prepared using identical amounts of water (section 3.3), similar granulation speeds and times (section 4.3), and that the dried granules should be size standardised prior to testing (section 5.3).

12.2 Materials and Methods

Granules were prepared batchwise using 150 g Emcocel 50M (lot number 8259, Edward Mendell Co. Inc., Patterson, New York, U.S.A.) with 105 g distilled water, which corresponded to 41.2 % $^{w}/_{w}$ water in the final wet mass, according to the general method described in section 3.2.1. In addition, granulation was carried out using aqueous solutions or suspensions containing selected 'additives'. Fluids containing each additive for granulating 150 g MCC were prepared in such a manner so as to provide the chosen concentration of additive, accurately weighed to ± 0.0001g, in 105 g distilled water. This experimental protocol enabled the weight of water used in the preparation of all granule types to be kept constant, although the weight of granulation fluid varied. This was considered important since it resulted in the same proportions of water available for interaction with MCC for granules prepared with each concentration of additive and for granules prepared without an additive. The additives used and the concentrations in the granulation fluid at which they were used are given in table 12.1. With the exception of granulation fluids containing gelatinised maize starch, fluids were prepared at ambient temperature and allowed to stand for 15-20 minutes before commencing granulation which was considered to ensure uniform dissolution / hydration of the additives. Two methods were investigated for preparation of granulation fluid containing maize starch: a) dispersion of ungelatinised maize starch in distilled water at ambient temperature as described above, and b) gelatinisation of maize starch in the granulation fluid. Method b) involved an initial dispersion of the required amount of maize starch in 105 g distilled water followed by gentle heating with continuous stirring until boiling.

Boiling was continued for 5 minutes to disrupt any remaining opaque particles of ungelatinised starch. Following cooling to room temperature, sufficient distilled water was added to the starch gels to compensate for water lost by evaporation during heating.

Granules were wet screened, dried and size standardised using the methods described in section 3.2.2. It was assumed that the additive was homogeneously distributed and was therefore uniformly present in all particle sizes of granules. With this assumption, the percentage of additive in the dried granules is given in table 12.1. In addition, sets of control granules were prepared by blending water-only granulated MCC, size standardised as above, with either ungelatinised maize starch powder or dried gelatinised maize starch powder. The latter was prepared by gelatinisation as above and milling and sieving to produce a particle size less than 125 μm. The final concentration of starch in these control samples of dried granules was equivalent to that in the granules prepared with ungelatinised and gelatinised starch in the granulation fluid (table 12.1).

Compaction and mechanical testing of tablets was performed as described in sections 2.2.8 and 2.2.9 without additional vibration of the feed shoe since all granule types were found to possess adequate flow characteristics. The relative influence of the presence of additives in the granulation fluid or added after preparation of dried granules was assessed from tablet tensile strength and corrected work of failure profiles as a function of upper punch force.

12.3 Results and discussion

12.3.1 Congo Red

Congo Red (sodium diphenylbisazobisnaphthylamine-4-sulphonate) is a reddish-brown powder. Solutions have general chemical use as a pH indicator and may be used intravenously as a haemostatic and to estimate blood volume. Higgins & McKenzie (1963) reported that approximately one-third of the loss in paper strength resulting from hornification due to intermediate drying of cellulose pulp could be prevented by performing the intermediate drying from a 0.20 % solution of Congo Red.

In comparison with granules prepared using water only, granulation using a 0.20 $\%^{w}/_{w}$ solution of Congo Red yielded granules with generally inferior compactibility as assessed by the strength and toughness of tablets produced

Table 12.1 Materials used as additives in the granulation fluid, together with the proportions in which they were used

Additive (for supplier and further details see notes below)	Additive (g) per 105 ml water	Concentration of additive in granulation fluid ($\%^{w}/_{w}$)	Equivalent concentration of additive in dried granules ($\%^{w}/_{w}$)
Congo Red[1]	0.21	0.20	0.14
	2.10	1.96	1.38
Era Tab[2]	2.00	1.87	1.32
Era Gel[3]	2.00	1.87	1.32
Rice Starch[4]	2.00	1.87	1.32
Maize starch[5], as received	0.525	0.50	0.35
(ungelatinised)	1.05	0.99	0.70
	2.00	1.87	1.32
	2.10	1.96	1.38
	5.25	4.76	3.38
Maize starch[5], gelatinised	0.525	0.50	0.35
	1.05	0.99	0.70
	2.10	1.96	1.38
	5.25	4.76	3.38
Glycerol[6]	2.10	1.96	1.38
	10.50	9.09	6.54
Maltodextrin[7]	2.10	1.96	1.38
	10.50	9.09	6.54
Sodium lauryl sulphate[8]	0.105	0.10	0.07
	0.525	0.50	0.35
	5.25	4.76	3.38
	10.50	9.09	6.54

Table 12.1 (continued)

Supplier and further details, where appropriate and available, of the 'additives' used:

[1] Thornton & Ross, Hudersfield, U.K.

[2] Erawan Pharmaceutical Research and Laboratory Co., Ltd., Bangkok, Thailand. Era Tab is described by the manufactures as a direct compression excipient based on rice starch

[3] Erawan Pharmaceutical Research and Laboratory Co., Ltd.. Era Gel is described by the manufactures as a wet granulation binder based on rice starch

[4] Erawan Pharmaceutical Research and Laboratory Co., Ltd.

[5] Batch number GC 80, BDH Chemicals, Poole, Dorset, U.K.

[6] BDH Chemicals, Poole, Dorset, U.K.

[7] Grade; 20 D.E., Snowflake, Cerestar Ltd., London, U.K.

[8] BDH Chemicals, Poole, Dorset, U.K.

(figure 12.1). However, increasing the concentration of Congo Red in the granulation fluid to 1.96 $\%^{w}/_{w}$ resulted in granules which exhibited similar compactibility to those prepared using water only (figure 12.1). Granulation with 0.20 and 1.96 $\%^{w}/_{w}$ solutions of Congo Red resulted in tablets which were light pink and dark pink/red respectively.

Higgins & McKenzie (1963) suggested that Congo Red may adsorb onto the microfibrillar surface of cellulose pulp fibres preventing intra- and interfibre cellulose - cellulose hydrogen bonding. On repulping it was proposed that the reversibility of the additive - cellulose bonds resulted in the additive largely desorbing from cellulose. Thus, the hydroxyl groups on the fibres were considered to have been partially protected from forming irreversible bonds during the intermediate drying stage, resulting in fibres with a higher flexibility and bonding

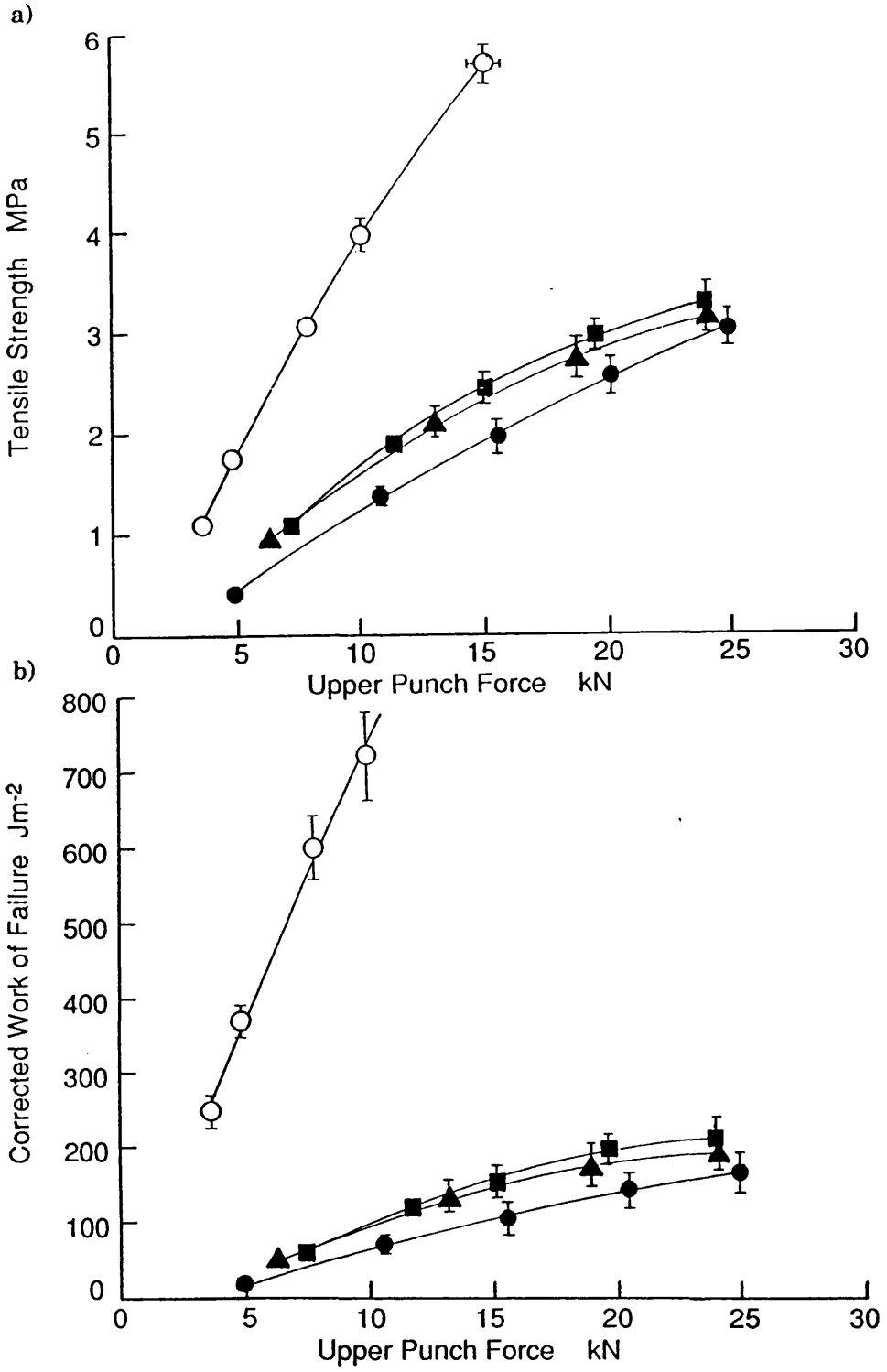


Figure 12.1 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules prepared with a solution of Congo Red. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: O
Granules: i) Granules prepared without an additive; ■ ii) Granules prepared using a 0.20 $\%^{w}/_{w}$ solution of Congo Red; ● iii)Granules prepared using a 1.96 $\%^{w}/_{w}$ solution of Congo Red; ▲

capability in comparison with fibres dried from water in the absence of the additive before repulping. However, despite repeated washing, the Congo Red was found to be incompletely removed from the pulp prior to the final drying stage (Higgins & McKenzie, 1963). This suggests that the adsorption of Congo Red onto cellulose was partially irreversible, or that dye molecules were entrapped in hornified fibre regions. Britt (1963) reported that the tensile strength of filter paper was unaffected when the paper was dipped in an aqueous solution of 0.5 % Congo Red before drying, suggesting that the presence of adsorbed dye during the drying stage did not interfere with fibre bonding.

In the present study the addition of Congo Red to the granulation fluid was found to have either no effect (1.96 $\%^{w}/_{w}$ additive concentration) or a detrimental effect (0.20 $\%^{w}/_{w}$ additive concentration) on granule compactibility. Elsewhere in the present study, the theory that wet granulation results in a reduction in the compactibility of MCC by causing intragranular bonding by quasi-hornification has been developed. This theory, taken together with the work reported by Higgins & McKenzie (1963) suggests that the presence of Congo Red in the granulation fluid might reduce the loss in compactibility following wet granulation. The reasons why this did not occur are open to speculation. It is possible that because unlike the materials prepared by Higgins & McKenzie (1963) the additive was not removed from the cellulosic material prior to drying, the degree of intraparticulate bonding was not reduced by the presence of Congo Red, and may even have been slightly increased in the case of granulation with a 0.20 $\%^{w}/_{w}$ solution. The proposal that Congo Red does not reduce the strength or degree of intraparticulate bonding is consistent with the results of Britt (1963), although in the present study it was found that a low concentrations (0.20 $\%^{w}/_{w}$) of additive, quasi-hornification apparently increased slightly.

It is also possible that increasing the concentration of Congo Red in the granulation fluid to greater than 1.96 $\%^{w}/_{w}$ may result in further increases in the strength and toughness of tablets produced. However, further investigation of this additive was considered of limited interest since the effect of Congo Red on the compactibility of MCC in the theoretically appropriate concentrations was small, and because of the undesirable effect of the additive on tablet colour even at low concentrations.

12.3.2 Starch and starch products

Starch is a naturally occurring material, being composed of two main polysaccharides: amylose and amylopectin. The proportions of the two polysaccharides vary with the biological source. Starch granules are insoluble in cold water. However, as the temperature of an aqueous suspension of starch is increased granules burst forming a starch paste or gel.

Preparation of MCC granules with granulation fluids containing 1.87 $\%^{w}/_{w}$ each of one of four starch products: Era Tab; Era Gel; rice starch (ungelatinised) and maize starch (ungelatinised); resulted in an improvement in the granule compactibility in comparison with granules prepared from water alone (figure 12.2). The greatest beneficial effect on tablet strength and toughness was observed using Era Tab in the granulation fluid. Era Tab is described by the manufacturers as insoluble "chemically and physically modified rice starch" which has "excellent compressibility" and is marketed as a direct compression excipient. However, further information regarding its exact physico-chemical nature was not provided by the manufacturers. Granulation with suspensions of either Era Gel, rice or ungelatinised maize starches produced tablets having similar strength and toughness (figure 12.2.). The improvement in compactibility of MCC following granulation using Era Gel, rice starch or ungelatinised maize starch was only approximately half that found with Era Tab (figure 12.2). Era Gel is described by the manufacturers as pregelatinised rice starch and suggested by them to be useful as a wet granulating binder.

Modification of starch to produce Era Tab may result in less stress relaxation and less elastic recovery compared with the other starches, thereby promoting enhanced tablet compactibility when included as an additive with MCC at a concentration of 1.87 $\%^{w}/_{w}$. However, since information regarding the methods of modification and production of Era Tab and Era Gel is unavailable for commercial reasons, further investigation of the use of these products was considered beyond the scope of the present study. Additional investigations regarding the effect of starch in the granulation fluid on granule compactibility were performed using maize starch.

The compaction force - tablet strength and toughness profiles for granules prepared using suspensions of maize starch of various concentrations between

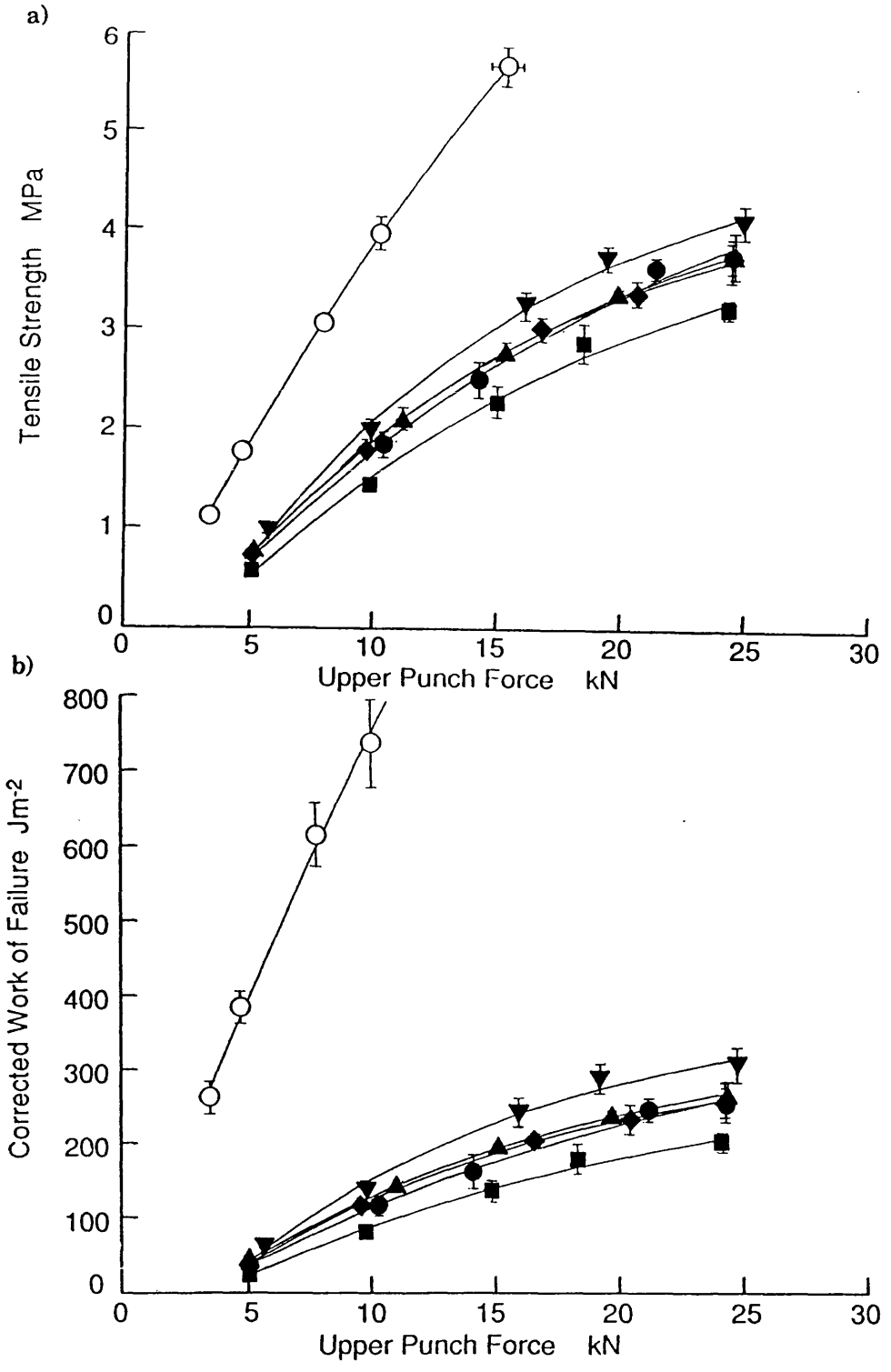


Figure 12.2 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules containing intragranular starch. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: O
Granules: i) Granules prepared without an additive; ■
ii) Granules prepared using a 1.87 $\%^{w}/_{w}$ suspension of Era Tab; ▼
iii) Granules prepared using a 1.87 $\%^{w}/_{w}$ suspension of Era Gel; ▲
iv) Granules prepared using a 1.87 $\%^{w}/_{w}$ suspension of ungelatinised maize starch; ●
v) Granules prepared using a 1.87 $\%^{w}/_{w}$ suspension of rice starch; ◆

0.50 and 4.76 $\%^{w}/_{w}$ are presented in figure 12.3. Granulation with a 4.76 $\%^{w}/_{w}$ suspension of maize starch resulted in a marginal and perhaps statistically insignificant improvement in compactibility in comparison with granules prepared with distilled water only (figure 12.3). However, reducing the concentration of starch in the granulation fluid to 1.96, 0.99 and 0.50 $\%^{w}/_{w}$ resulted in an improvement in granule compactibility. However, the overlap of the 95 % confidence interval limits for the profiles for tablets prepared from granules with the latter three concentrations of starch presents difficulties in assessing the significance of their relative effects on granule compactibility.

Higgins & McKenzie (1963) reported that by incorporation of 1-2 % wheat starch into pulps before drying, on repulping and papermaking the strength of paper produced was greater than that prepared from a similar pulp which had never been dried. The starch was not, however, completely removed on repulping, and it was suggested that the beneficial effect of starch on paper strength may be due to its function as an adhesive during final papermaking. However, it was also proposed that starch may form reversible bonds with cellulose during intermediate drying, thereby resulting in retention of fibre conformability following repulping as described for Congo Red in section 12.3.1 above.

It was considered that in the present study the inclusion of starches in the granulation fluids exerted a beneficial influence on MCC granule compactibility by reducing intragranule bonding and thereby facilitating granule deformability on compaction, and / or by acting as an intergranule binder. The effect of starch on the mechanical properties of tablets produced from wet granulated MCC was further investigated by preparation of tablets from dried granules prepared using MCC and water alone to which had been added starch to give equivalent proportions of MCC and starch as those for granules prepared using starch suspensions as the granulation fluid. Addition of starch to dried granules had a marginal and possibly detrimental effect on granule compactibility (figure 12.4). Thus, it was suggested that the beneficial effect of granulation with starch suspensions on granule compactibility was exerted by the presence of the additive within the granules rather than by acting as an intergranule binder. Although not proven experimentally, it is possible that starch reduces intragranular bonding by acting as a bulking agent which, by swelling during drying at elevated temperatures, disrupts intragranule bonding. Alternatively or additionally the

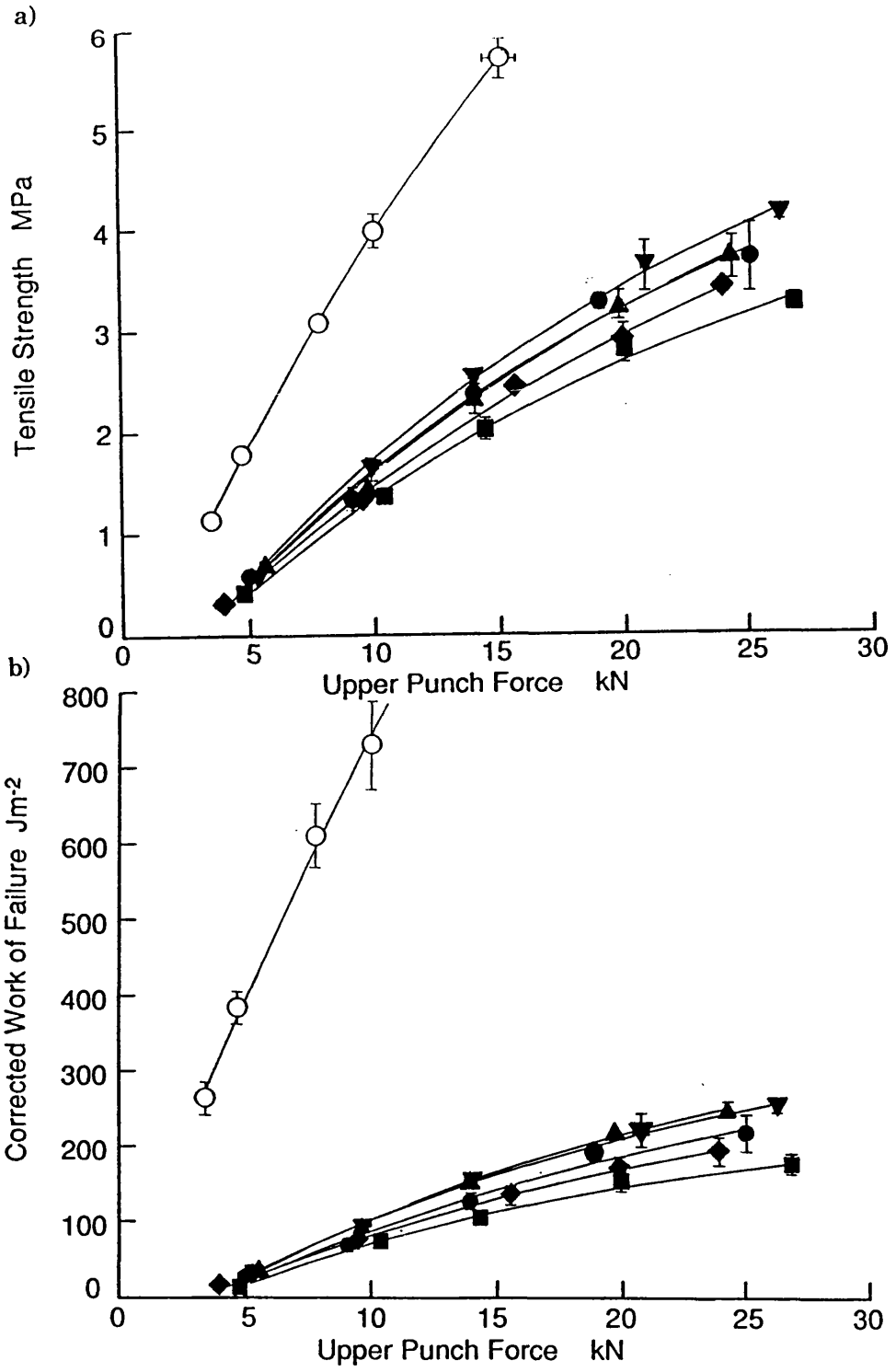


Figure 12.3 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules containing intragranular ungelatinised maize starch. Note: Error bars represent 95% confidence limits.

Key: Ungranulated MCC: ○

Granules: i) Granules prepared without an additive; ■

ii) Granules prepared using a 0.50 $\%^{w}/_{w}$ suspension of maize starch; ▲

iii) Granules prepared using a 0.99 $\%^{w}/_{w}$ suspension of maize starch; ▼

iv) Granules prepared using a 1.96 $\%^{w}/_{w}$ suspension of maize starch; ●

v) Granules prepared using a 4.76 $\%^{w}/_{w}$ suspension of maize starch; ◆

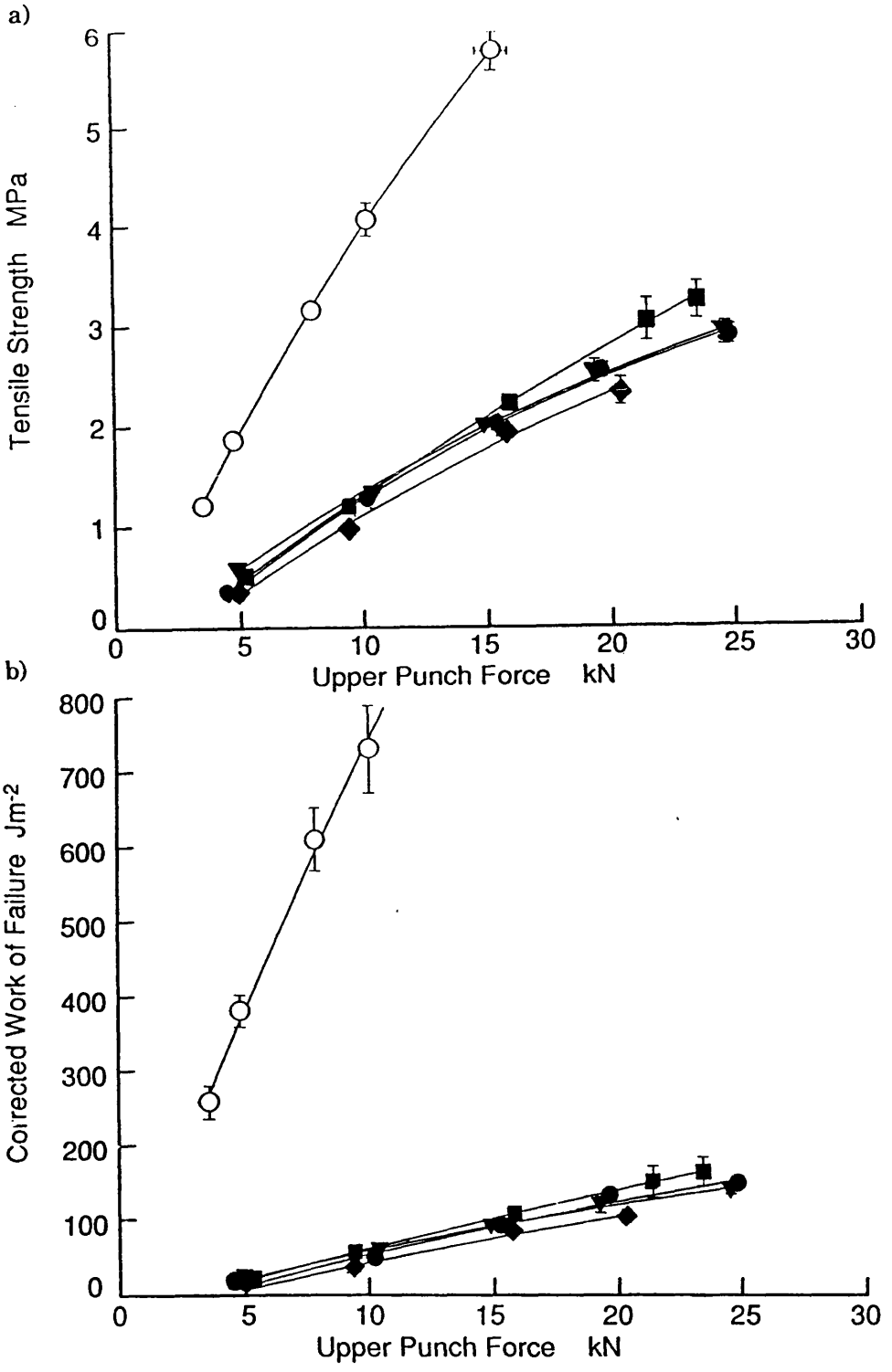


Figure 12.4 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive with various proportions of extragranular ungelatinised maize starch. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: O
Water-granulated MCC containing: i) 0 $\%^{w}/_{w}$; ■ ii) 0.70 $\%^{w}/_{w}$; ▼
iii) 1.38 $\%^{w}/_{w}$; ● iv) 3.38 $\%^{w}/_{w}$; ◆ extragranular ungelatinised starch.

starch may exert its beneficial action by forming weaker bonds with cellulose microcrystal surfaces than would be formed between pure cellulose microcrystal surfaces. Further, the results indicate that such effects outweighed any detrimental effect of starch on cellulose - cellulose bonding upon compaction.

Gelatinised starch is frequently used as an adhesive binder in wet granulations as a means of improving granule compactibility. The effects of granulating MCC with solutions containing gelatinised maize starch at a series of concentrations between 0.50 and 4.76 $\%^{w}/_{w}$ are presented in figure 12.5. Increasing the concentration of gelatinised maize starch in the granulation fluid from 0.5 to 4.76 $\%^{w}/_{w}$ resulted in a progressive reduction in the strength and toughness of tablets produced. However, addition of dried gelatinised maize starch to dried MCC granules granulated with water alone resulted in relatively little reduction in granule compactibility (figure 12.6). Thus, the detrimental effect of gelatinised maize starch appears to be dependant on its presence within granules or during wet massing. It is speculated that the presence of gelatinised maize starch in the granulation fluid increased the viscosity of the granulation fluid thereby increasing wet granule cohesion. Further, by acting as a wet granulation binder, on drying, the greater wet granule cohesion resulted in increased granule strength and reduced granule deformability and thus reduced opportunity for bonding upon compaction.

12.3.3 Glycerol

It has been reported that between half and virtually all of the loss in paper strength caused by intermediate pulp drying prior to repulping and paper making could be prevented by performing the intermediate drying from an aqueous solution of 20 % glycerol, although this effect was found to be dependant on the pulp source and repulping conditions employed (Higgins & McKenzie, 1963). Glycerol is a hygroscopic, clear, colourless liquid. Granulation with a 1.96 $\%^{w}/_{w}$ solution of glycerol resulted in a marginal although probably insignificant reduction in the strength and work of failure of tablets produced in comparison with granules prepared using distilled water only (figure 12.7). Increasing the concentration of glycerol in the granulation fluid to 9.09 $\%^{w}/_{w}$, however, resulted in a significant decrease in granule compactibility in comparison with granules prepared in the absence of an additive (figure 12.7). Furthermore, the compaction force - tensile strength / corrected work of failure

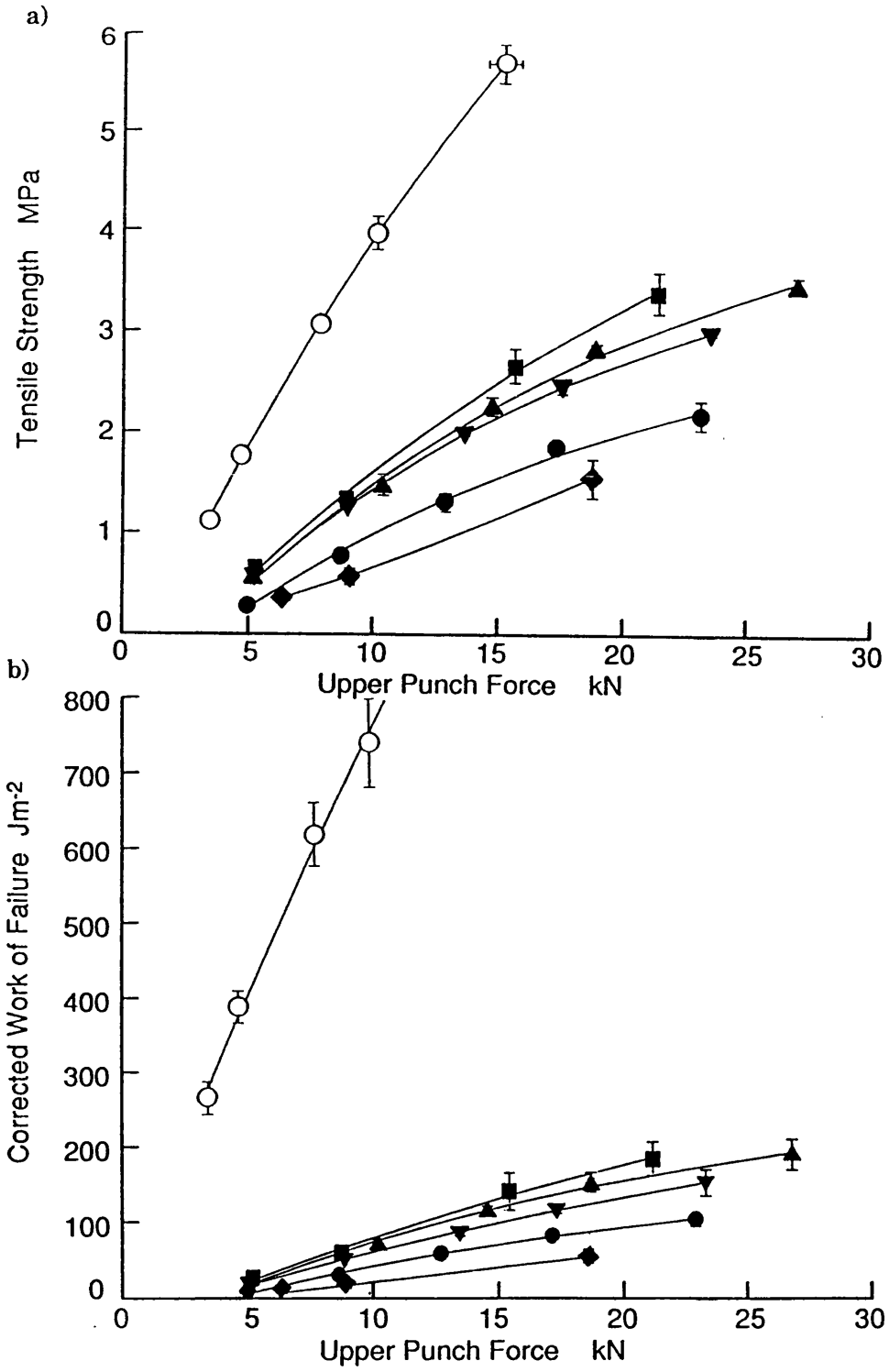


Figure 12.5 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules containing intragranular gelatinised maize starch. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: O
Granules: i) Granules prepared without an additive; ■
ii) Granules prepared using a 0.50 $\%^{w}/_{w}$ solution of gelatinised starch; ▲
iii) Granules prepared using a 0.99 $\%^{w}/_{w}$ solution of gelatinised starch; ▼
iv) Granules prepared using a 1.96 $\%^{w}/_{w}$ solution of gelatinised starch; ●
v) Granules prepared using a 4.76 $\%^{w}/_{w}$ solution of gelatinised starch; ◆

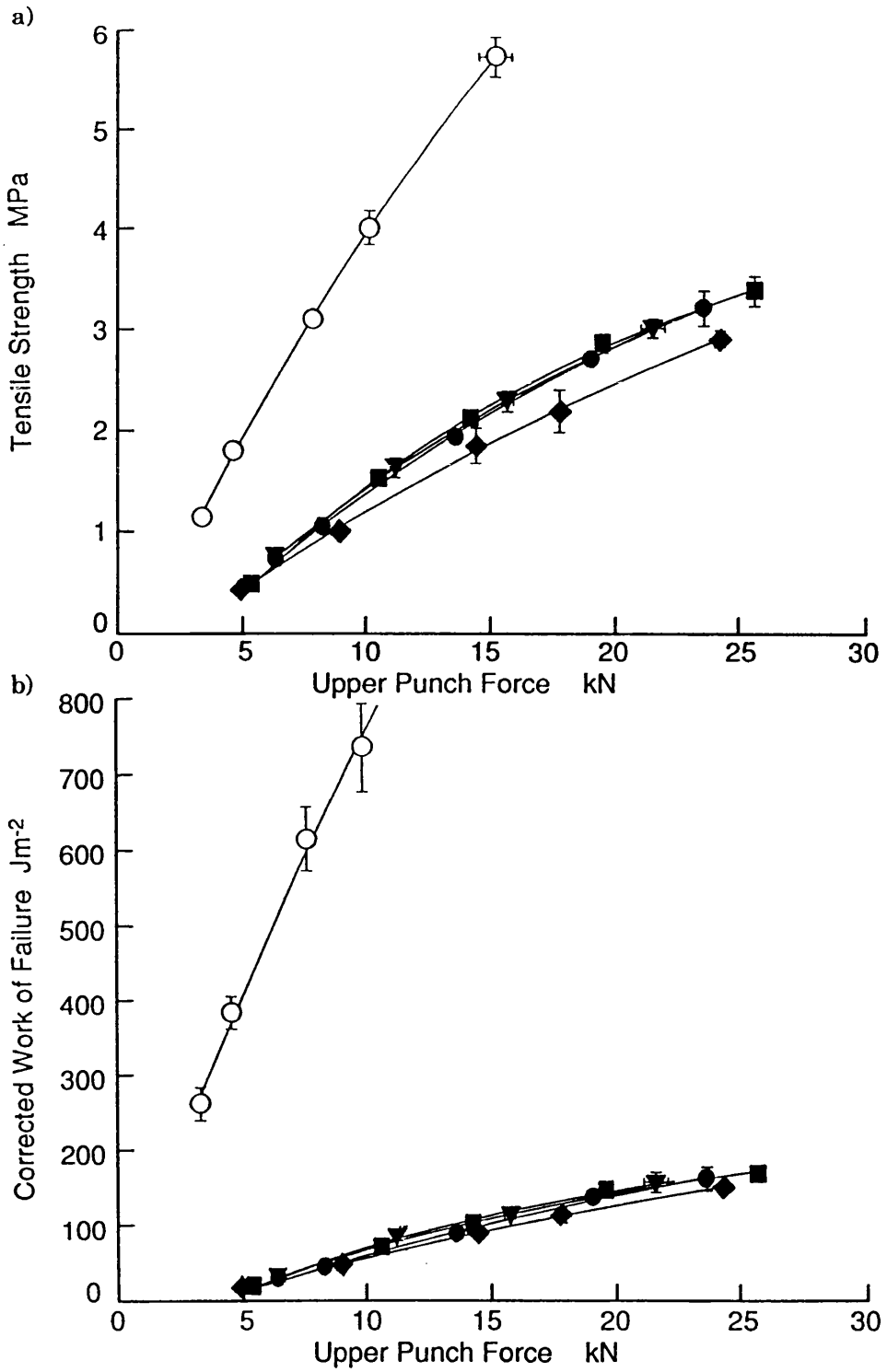


Figure 12.6 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive with various proportions of extragranular gelatinised maize starch. Note: Error bars represent 95% confidence limits.

Key: Ungranulated MCC: ○

Water-granulated MCC containing: i) 0 $\%^{w}/_{w}$; ■ ii) 0.70 $\%^{w}/_{w}$; ▼

iii) 1.38 $\%^{w}/_{w}$; ● iv) 3.38 $\%^{w}/_{w}$; ◆ extragranular gelatinised starch.

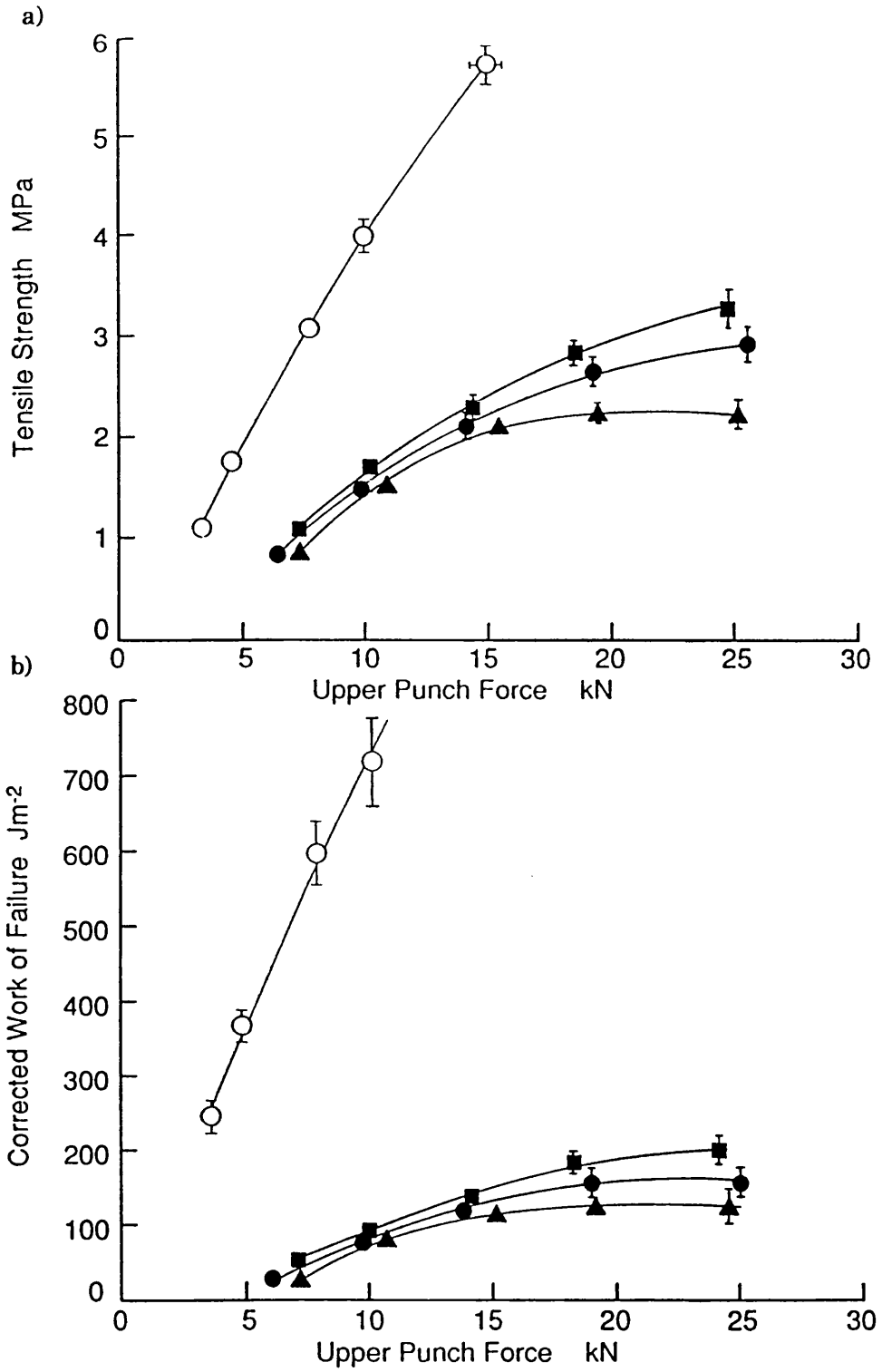


Figure 12.7 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules prepared with a solution of glycerol. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: O
Granules: i) Granules prepared without an additive; ■ ii) Granules prepared using a 1.96 $\%^{w}/_{w}$ solution of glycerol; ● iii)Granules prepared using a 9.09 $\%^{w}/_{w}$ solution of glycerol; ▲

profiles for tablets prepared from granules prepared using 9.09 $\%^{w}/_{w}$ glycerol levelled off after a compaction force of approximately 15 kN.

Higgins & McKenzie (1963) suggested that glycerol may form reversible bonds with cellulose, thereby conferring a degree of protection against hornification by a mechanism similar to that proposed for Congo Red as discussed in section 12.3.1. The reasons for the apparent inability of glycerol to inhibit the detrimental effects of wet granulation on the compactibility of MCC found in the present study are uncertain. However, since the glycerol was not removed from the wet granules prior to compaction, it is possible that the additive increased the dried granule strength, thereby reducing the deformability upon compaction. Alternatively, if glycerol did improve granule deformability, this effect could have been outweighed by its presence reducing intergranular bonding once surfaces had been brought into close proximity. Furthermore, the levelling off of the compaction force - tensile strength / corrected work of failure profiles after a compaction force of 15 kN suggests that hydrodynamic resistance of the additive, which is a liquid under ambient conditions, may have reduced granule consolidation at compaction pressures greater than 15 kN. The use of higher sugar alcohols such as mannitol or sorbitol, which are solid under ambient conditions, as granulation additives may enable granule compactibility to be improved in comparison with granules prepared using glycerol. However, if improvements in granule deformability be outweighed by a reduction in the intergranule bonding following compaction, sugar alcohols would not preserve compactibility of MCC following wet granulation.

12.3.4 Maltodextrin

Maltodextrins are prepared by controlled acidic or enzymatic hydrolysis of starch. By varying the extent of hydrolysis the average degree of polymerisation may be altered. Maltodextrins are classified according to their dextrose equivalent value (D.E.), 20 D.E. being high and indicating a high reducing sugar content and therefore a low average degree of polymerisation. Conversely, a low D.E. value such as 5 indicates a high average degree of polymerisation (Li & Peck, 1989). Parrott (1989) has evaluated a commercial spray dried maltodextrin product for use as a direct compression excipient. The maltodextrin was shown to exhibit high compactibility although inferior to that for ungranulated MCC. An increase in the degree of polymerisation has also been reported to reduce the compressibility of

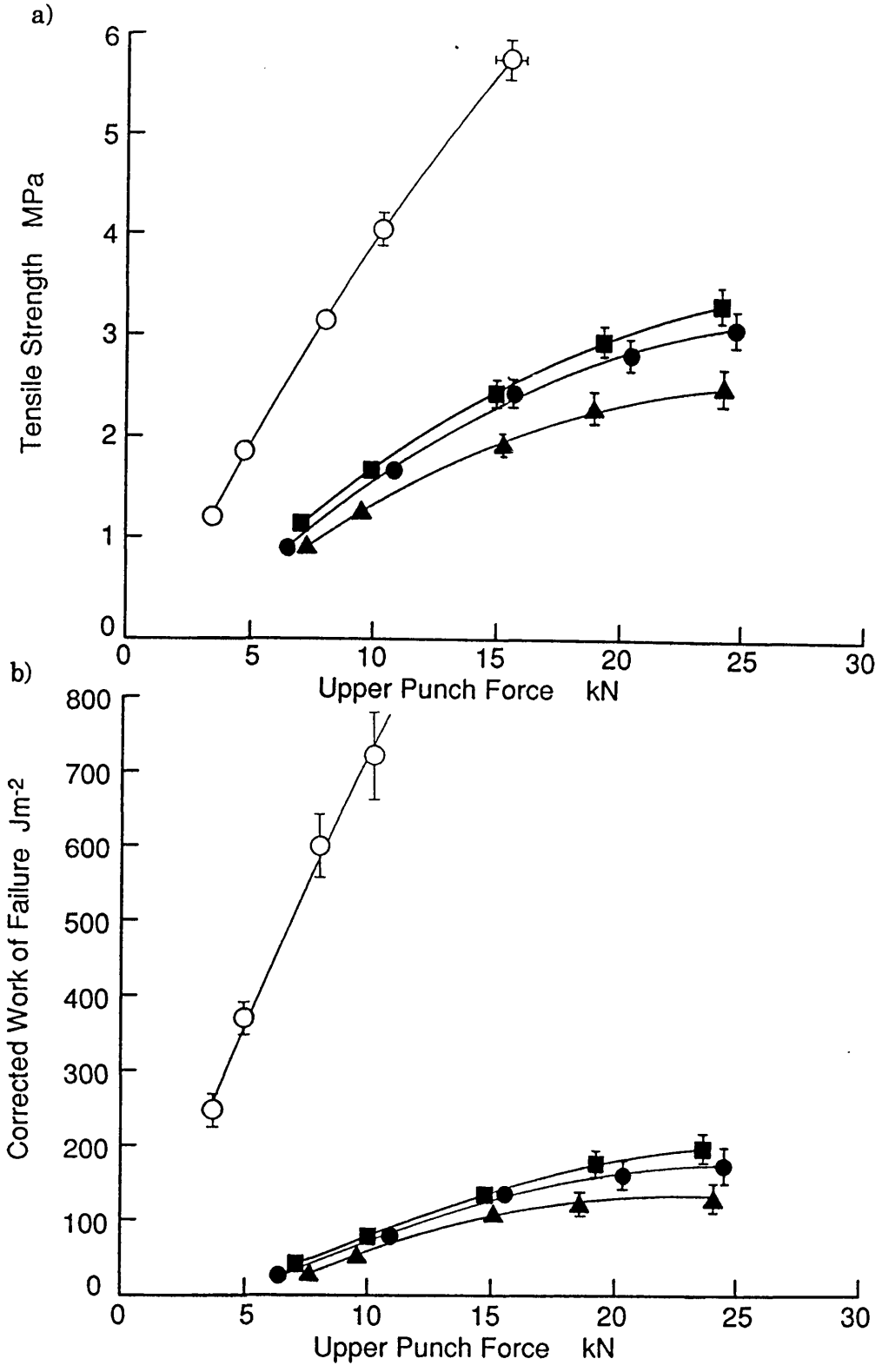


Figure 12.8 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules prepared with a solution of maltodextrin. Note: Error bars represent 95% confidence limits.
Key: Ungranulated MCC: O
Granules: i) Granules prepared without an additive; ■
ii) Granules prepared using a 1.96 $\%^{w}/_{w}$ solution of maltodextrin; ●
iii)Granules prepared using a 9.09 $\%^{w}/_{w}$ solution of maltodextrin; ▲

maltodextrins (Li & Peck, 1989).

Higgins & McKenzie (1963) reported that approximately half the loss in paper strength resulting from intermediate drying of cellulose pulp could be prevented by performing the intermediate drying in a solution containing 10 % water soluble starch dextrins. It was suggested that dextrins may protect hydroxyl groups from hornification as described for Congo Red in section 12.3.1 above. In the present study, granules prepared using a 1.96 $\%^{w}/_{w}$ maltodextrin solution yielded tablets having similar or perhaps marginally reduced tensile strength and toughness in comparison with granules prepared in the absence of an additive (figure 12.8). Granulation using a 9.09 $\%^{w}/_{w}$ solution of maltodextrin however resulted in significant decrease in granule compactibility. The lower effectiveness of maltodextrin in comparison with dextrin may in some way be associated with its higher molecular weight. The detrimental effect of the addition of maltodextrin to the granulation fluid on granule compactibility found in the present study may also be due to the presence of maltodextrin in the granules increasing granule strength by acting as a wet granulation binder, thereby reducing granule deformability and subsequent intermicrocrystal bonding, or by directly inhibiting the formation of intergranular hydrogen bonds.

12.3.5 Sodium lauryl sulphate

It has been shown elsewhere in the present study that freeze drying of granules (section 6.3.1) or exchanging the water used to granulate MCC with an organic solvent (section 7.4) before drying resulted in an improvement in granule compactibility in comparison with granules dried by evaporation of water, perhaps by reducing the surface tension of the drying liquid. Furthermore, as discussed in section 1.5.5.2, it has been demonstrated by other workers that granulation of MCC with ethanol results in granules with a higher compactibility in comparison with water granulated MCC. Further to the discussion in section 3.4.1, it was hypothesised that a reduction in surface tension effects during granule drying may improve granule compactibility by reducing the degree of intragranule collapse and thus bonding.

In the present study sodium lauryl sulphate was used to reduce the surface tension of the granulation fluid. The latter is a pharmaceutical excipient which is a less pure form of the anionic surface active agent sodium dodecyl sulphate,

$CH_3(CH_2)_{11}.SO_4^-$ Na^+. Granulation of MCC with an aqueous solution of 0.50 $\%^w/_w$ sodium lauryl sulphate resulted in a significant, although modest, improvement in the strength and toughness of tablets produced in comparison with granules prepared using distilled water only (figure 12.9). However, a reduction in the concentration of the surfactant in the granulation fluid to 0.10 $\%^w/_w$, or an increase in the concentration of the surfactant to 4.76 and 9.09 $\%^w/_w$ largely negated this beneficial effect on granule compactibility (figure 12.9).

Higgins & McKenzie (1963) reported that approximately half to one-third of the loss in paper strength caused by pulp drying prior to repulping and paper making could be prevented by performing the intermediate drying from a 10 % solution of 'Comprox', a commercial sodium alkyl sulphate detergent. A reduction in the concentration of surfactant in solution to 1 % resulted in a small decrease in its beneficial effect on the final paper strength. Treiber & Abrahamson (1972) have also reported that drying of cellulose pulp in the presence of a surfactant (type not specified) resulted in the secondary fibres having an intermediate swelling capacity compared with undried fibres and secondary fibres dried without surfactant. It was suggested that by reducing the surface tension of water during the intermediate drying stage, the surfactant reduced inter- and intrafibre collapse and thus intrafibre bonding (Higgins & McKenzie, 1963). This explanation may also account for the modest improvement in compactibility resulting from the addition of 0.50 $\%^w/_w$ sodium lauryl sulphate to the granulation fluid reported in the present study (figure 12.9). As the concentration of a surfactant is increased from zero, the surface tension is reduced, eventually leveling off at a concentration roughly equivalent to the critical micelle concentration (Attwood & Florence, 1983a). The critical micelle concentration of sodium lauryl sulphate in water is 8.2×10^{-3} mol l^{-1} at 25°C (Attwood & Florence, 1983b) which is approximately equivalent to a 0.23 $\%^w/_w$ solution. Thus, as the concentration of sodium lauryl sulphate in the granulation fluid is increased from 0.10 to 0.50 $\%^w/_w$, the surface tension of the granulation fluid will decrease. This may account for the beneficial effect of granulating with 0.50 $\%^w/_w$ solution in comparison with a 0.10 $\%^w/_w$ solution. However, in contrast to the results of Higgins & McKenzie (1963), in the present study it was found that increasing the concentration of surfactant in the granulation fluid to an amount substantially above the critical micelle concentration resulted in a decrease in its beneficial effect on the strength and toughness of tablets produced (figure 12.9). Higgins &

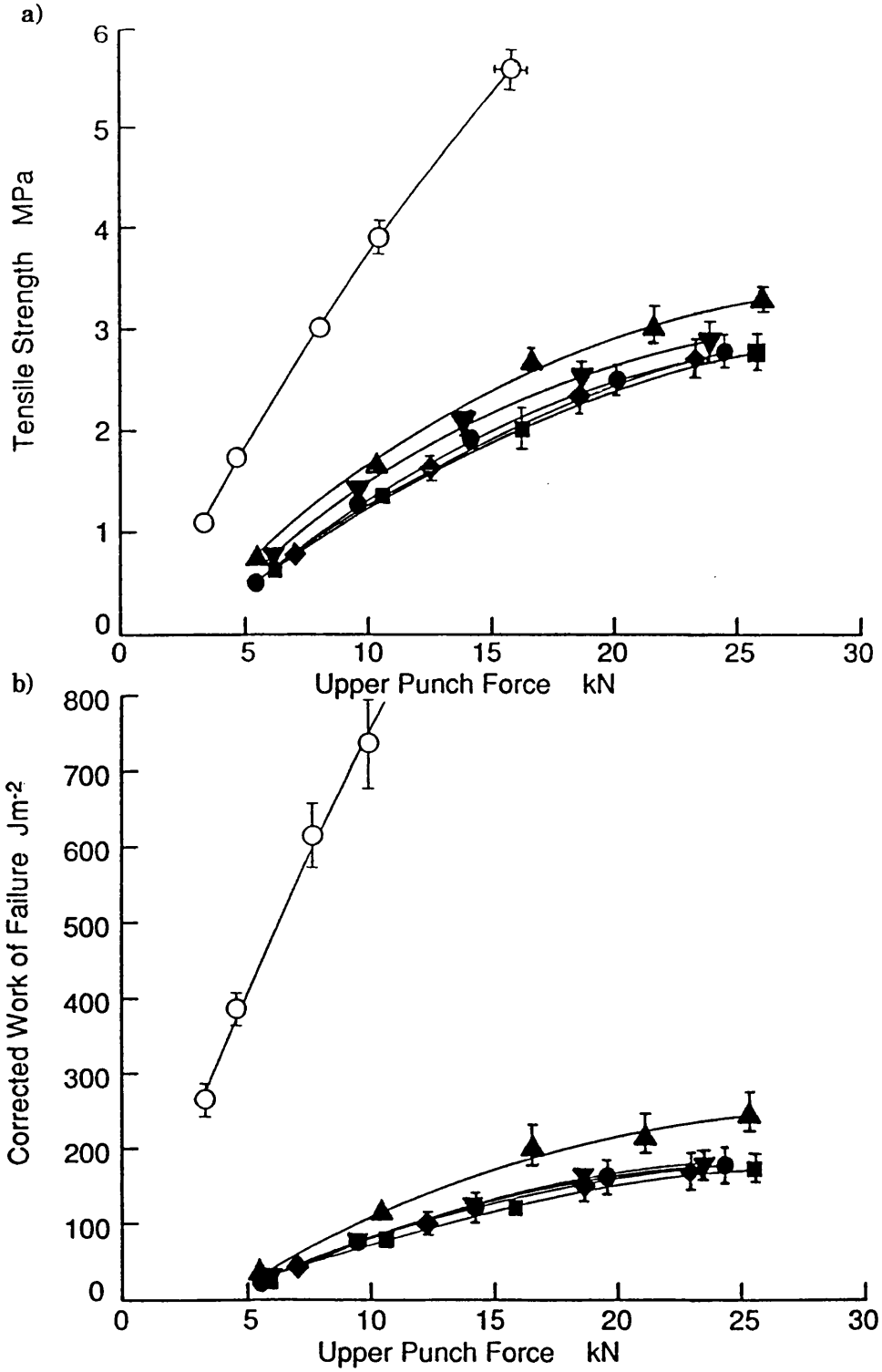


Figure 12.9 Relationship between a) tensile strength, and b) corrected work of failure, and compaction force for tablets prepared from ungranulated MCC, granules prepared without an additive, and granules prepared with a solution of sodium lauryl sulphate (SLS). Note: Error bars represent 95% confidence limits.

Key: Ungranulated MCC: ○

Granules: i) Granules prepared without an additive; ■

ii) Granules prepared using a 0.10 $\%^{w}/_{w}$ solution of SLS; ▼

iii)Granules prepared using a 0.50 $\%^{w}/_{w}$ solution of SLS; ▲

iv) Granules prepared using a 4.76 $\%^{w}/_{w}$ solution of SLS; ●

v)Granules prepared using a 9.09 $\%^{w}/_{w}$ solution of SLS; ◆

McKenzie (1963) stated that complete removal of the surface active agent during repulping is necessary in order to achieve maximum benefit on the resulting paper strength since the presence of a surfactant may reduce interfibre bonding by exerting an effect on the fluid to be dried during the final papermaking stage. It is possible that the presence of sodium lauryl sulphate in the final granules interferes with intermicrocrystal bonding upon compaction, although it is unlikely that this effect is due to its ability to reduce surface tension since granules are compacted in the dry state. It is considered more likely that cellulose - surfactant bonds are weaker than cellulose - cellulose bonds, but although the deformability of granules may be increased by the inclusion of surfactant in the granulation fluid, this effect is outweighed, particularly at higher concentrations of the additive, by its interference with intergranular bonding within the tablet.

The influence of concentrations of sodium lauryl sulphate between 0.10 and 0.50 $\%^{w}/_{w}$ on granule compactibility, and the effect of alternative surfactants warrants further investigation as the above results suggest that close to the critical micelle concentration it may be possible that the reduction in intragranule bonding may be more significant than the reduction in bonding within the tablet upon compaction.

12.4 Further discussion

In addition to the considerations discussed above, differences between the compactibility of granules prepared using water only and using granulation fluids containing various additives may be partially or wholly attributed to the effect of the additive on the surface tension (already discussed for sodium lauryl sulphate in section 12.3.5) and viscosity of the granulation fluid since it has been suggested that a reduction in granulation fluid surface tension and / or dynamic viscosity results in lower cohesive forces in the wet granules (Wells & Walker 1983; Parker et al, 1990, 1991) which may result in a reduction in dry granule strength.

Chapter 13. Conclusions

Wet granulation was found to reduce the compactibility of MCC. The reduction in compactibility of MCC caused by granulation was not found to be related to the effect of granulation on particle size. It was thus considered that granulation altered the inherent physico-mechanical characteristics of MCC. However, the particle size distribution of granules was found to influence compactibility, and for this reason, where appropriate it was considered prudent to standardise granule particle size distributions.

As the granulation water level was progressively increased, the compactibility of MCC granules initially decreased. However, as the proportion of water was increased further, dried granule compactibility was found to increase. Granule compactibility reached a minimum when granules were prepared with approximately 40 $\%^{w}/_{w}$ water. Granule surface area, porosity and friability passed through a minimum and granule bulk density through a maximum at similar, although not identical, granulating fluid levels to that causing minimum compactibility. It was proposed that increasing the granulating fluid level up to 40 $\%^{w}/_{w}$ resulted in an increase in intragranule hydrogen bonding by a phenomenon termed quasi-hornification which arose from intraparticle collapse caused by surface tension effects. At higher granulating fluid levels it was proposed that intragranule collapse was partially opposed by intergranule surface tension forces. Further, the absence of co-attainment of minima and maxima for different MCC granule properties caused by varying the granulating fluid level suggested that the relationship between individual granule properties and degree of wet binding was complex.

Granule physico-mechanical characteristics were also found to be substantially affected by a) the speed and time for which the wet mass was agitated and b) subsequent storage time before drying. In general an increase in the 'interaction' of MCC with the granulating water resulting in a reduction in granule compactibility which was considered consistent with the theory that granulation reduced MCC compactibility by causing quasi-hornification. In addition, the drying technique used was found to affect the physico-mechanical characteristics of granules produced. For example, freeze drying and microwave-vacuum drying resulted in slightly improved compactibility in comparison with tray-dried granules. Again, the effect of drying technique on granule

compactibility could be interpreted in terms of the effect of drying technique on the degree of intragranule collapse and therefore bonding produced, although the effects of drying techniques on granule physical properties were less readily explained. De-watering by solvent exchange was found to markedly improve the compactibility of granulated MCC. It was considered that replacement of the granulating water with a fluid with a lower surface tension reduced intraparticle collapse upon drying and thus quasi-hornification. However, despite having a higher specific surface area available to nitrogen, solvent exchanged granules had inferior compactibility in comparison with ungranulated MCC. This further highlighted the complex relationship between the physical properties of MCC particles and their compaction characteristics.

Granulation was not found to have a significant effect on the solubility parameters of MCC. This suggested that granulation did not reduce MCC compactibility by altering the surface, and therefore bonding, characteristics of MCC, and further provided indirect evidence that granulation reduced MCC compactibility by some other mechanism such as alteration of the inherant deformation characteristics of MCC. In addition, unlike the effect of hornification on un-hydrolysed cellulose reported elsewhere, in the present study quasi-hornification of MCC caused by wet granulation was not found to reduce its water adsorbing - desorbing properties. Using water-adsorption microcalorimetry, subtle differences were observed between the kinetics of water adsorption and heat of water vapour adsorption by ungranulated and granulated MCC. The results suggested that during water vapour adsorption by granulated MCC, relatively more cellulose - cellulose bonds were disrupted in comparison with the case of water vapour adsorption by ungranulated MCC. The results were considered consistent with the theory that granulation caused quasi-hornification, and further that some of the intraparticle bonds formed were reversible on adsorption of water vapour.

The effect of wet granulation on the physico-chemical characteristics of MCC was also investigated using a variety of spectroscopic techniques. In general granulation was found to have a minimal effect on the physico-chemical characteristics of MCC. However, granulation appeared to alter the infra-red spectra obtained using attenuated total reflectance spectroscopy of MCC, an effect which warrants further investigation.

As indicated above, it was considered that many of the differences between the physico-mechanical characteristics of ungranulated and granulated MCC could be explained by the proposal of a theory of quasi-hornification, with granulation resulting in increased intraparticle hydrogen bonding. Attempts to reduce intragranule bonding by including 'additives' in the granulation fluid which were found by other workers to reduce hornification of cellulose fibres were only partially successful in improving granule compactibility. Of these materials ungelatinised starch and sodium lauryl sulphate were found to improve granule compactibility to a limited extent, and this was considered at least partly due to the influence of such additives in reducing intragranular collapse of MCC particles.

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Appendix i. Tableting properties of various microcrystalline celluloses.

M. Chatrath, J.N. Staniforth.

Transcript of paper presented at the A.P.V. conference on Tablet Excipients, Nuerenberg, Germany, Sept. 22-23, 1988.

Introduction

Since its introduction in the early sixties, microcrystalline cellulose (MCC) has been extensively used as an excipient in pharmaceutical dosage forms. MCC exhibits excellent compactibility enabling robust tablets to be formed which also disintegrate rapidly. A combination of these and other properties make MCC particularly valuable as a filler/binder for use in formulations prepared by direct compression [1,2]. MCC is also used in tablet formulations prepared by wet or dry granulation methods, and in formulations to be encapsulated.

Until recently, the only MCC materials widely available for use in pharmaceutical tableting were the grades of Avicel marketed by FMC. Other manufacturers have now introduced their own commercial forms of MCC, some of which, like Avicel, are available in more than one grade. Before discussing some of the differences between tableting grades and commercial brands, it would be useful to briefly examine the raw material cellulose, the processes involved in the manufacture of MCC, and some of the general properties of this material.

Section 1: Cellulose and the Manufacturing Process for MCC

Cellulose is a naturally occurring polymer composed solely of glucose units linked by a 1-4-β-glucosidic bond (Fig. 1). The linear cellulose chains exist in bundles termed microfibrils which are found spiralled in layers in plant cell walls (Fig. 2). Within each microfibril exists a high degree of three-dimensional internal bonding (Figs 3a and b). This results in an essentially crystalline structure, insoluble in water and largely inaccessible to reagents. However along the microfibril length also exists relatively weak regions which contain a lower degree of internal bonding. These are sometimes termed amorphous regions in accordance with the fringe micellar theory (Fig. 4), but are perhaps more correctly thought of as dislocations (Fig. 5) since it has been demonstrated that microfibrils contain a single phase structure [3,4].

The manufacturing process for MCC has been described for the Avicels [5,6], and is shown diagramatically in Fig. 6. The starting material is a high purity dissolving grade cellulose wood pulp which is subjected to controlled acid hydrolysis with agitation. The relatively accessible amorphous or dislocated regions are preferentially penetrated and hydrolysed by the acid and dissolved away, leaving microcrystals or chemically fragmented cellulose [7]. This is washed, filtered and spray-dried to produce a fine MCC powder. Many of the powder particles consist of randomly aggregated microcrystals held by hydrogen bonding, although some particles are larger pieces of microfibrils. Different grades of MCC can be produced by altering the hydrolytic and spray-drying conditions. Commercial forms other than Avicel are likely to be manufactured by a broadly similar process, although as will be discussed below, some variations probably occur.

Section 2: General Properties of MCC

Like the parent material cellulose, MCC possesses the desirable properties of being stable, generally regarded as safe, non-digestible and physiologically inert [7]. In addition, no incompatibilities have been reported [8], and the presence of MCC can in fact improve the stability of some actives [9]. The excellent compressibility of the material has been suggested to be due to slip planes and dislocations within particles, a direct result of the manufacturing process [5]. On application of a compressive force, elastic, time-dependent viscoelastic and plastic deformation occurs, the latter perhaps by particle fragmentation followed by rebonding [9,10]. During compaction, large surface areas of cellulose fragments are thus brought into close proximity. Interparticulate hydrogen bonding results in the formation of a robust compact, even under comparatively low compaction pressures [5,11]. Increasing the compaction pressure increases the amount of permanent deformation and interparitculate bonding, and so results in stronger, denser, more slowly disintegrating tablets [1,9,10,12]. In general terms even robust compacts exhibit rapid disintegration in water [5,9]. The disintegration mechanism is of capillary uptake of aqueous media which subsequently disrupts interparticulate hydrogen bonding [5,9,11]. However the disintegration and dissolution properties of formulations containing MCC is significantly affected by porosity, bond strength and the nature of other constituents [13,14]. Although sometimes reported as free flowing [1], MCC is generally regarded as possessing poor flow properties [2]. This has been attributed to the low bulk density, small size and irregular shape of the particles [9,12,15]. Addition of low concentrations of magnesium stearate slightly improves flow and decreases tablet weight variation [12] but by reducing interparticulate bonding, results in tablets of inferior strength which exhibit faster disintegration [12,13,14]. MCC also has the potential disadvantage of being hygroscopic [2], and when purchased, most grades and commercial forms contain around 5% sorbed moisture. Much of this moisture however is tightly bound to MCC and so unavailable for reaction with other ingredients in the formulation [16,17]. Sorption of moisture by tablets can reduce tablet strength and disintegration time [18,19].

Most of the work reported in the literature concerns the properties of MCC related to its use in direct compression formulations. Wet granulation although likely to improve flow properties, results in inferior compression and compaction properties perhaps because robust granules are formed which have increased resistance to deformation compared with MCC powder [20].

The manufacture and properties of MCC are further discussed by Lamberson and Raynor [5] and in a review article by Sixsmith [9].

Section 3: Comparative Properties of Different Grades of MCC

A summary of the principle differences reported between the Avicel grades is shown in table 1. Most of the grades of other commercial forms of MCC broadly correspond to Avicel grades PH-101 and PH-102 and will be termed types 1 and 2 respectively. General differences between grades are described below, the sole reason for particular reference being made to the Avicels is because the properties of this commercial form have been the most widely reported in the literature.

Some of the physical characteristics of the four grades of Avicel have been determined by Marshall and Sixsmith [21]. In each powder sample, two types of particles were noticed; one rod-shaped, the other an irregular mass.

Shape probably accounts for different values for the mean particle diameter and size distribution being obtained using different experimental methods. Although these workers found significant intraparticulate porosity [21] their results have been questioned [16]. The surface energies of particles in each grade were found to be similar [21], but the cohesion between particles, internal friction and the flow properties of each grade were found to differ [15]. These differences have been attributed to variations in mean particle size, shape and moisture content between the different grades [12,15]. Values for crystallinity [22] and the specific surface area as determined from nitrogen and moisture sorption [17] have also been found to vary slightly between grades.

With respect to compression and compaction properties, differences have also been noticed between grades [9,10,25]. In particular, the compaction mechanism of the fine-particle Avicel PH-105 grade has been found to be different from the other Avicel grades, and the disintegration properties significantly inferior [10,25]. The latter is perhaps due to tablets containing smaller interparticulate pores [25].

Considering the differences between MCC types 1 and 2, the particles in type 2 materials have a larger mean diameter and more agglomerated structure than those in type 1. Although some studies indicate little significant difference in tablet weight variation between the two grades [24] some studies show that type 2 materials exhibit higher packing densities, superior flow properties and less weight variation on tableting with [12,23] and without magnesium stearate [12]. Discrepancies can however be found in the literature concerning their comparative compaction properties. Most studies however indicate that type 1 materials form slightly stronger tablets than type 2 materials when compressed at the same relative pressures, particularly if the formulations contain magnesium stearate [5,23,24].

A study concerning the comparative compaction properties of the low moisture grades e.g. Avicel PH-103 with grades of MCC with a similar particle size distribution but higher moisture content e.g. Avicel PH-101, cannot be found in the literature. However reducing the moisture content of Avicel PH-101 has been found to result in tablets of inferior strength when compressed at the same pressure [19] or to the same relative density [18]. The weaker tablets exhibit correspondingly faster disintegration [19]. Hence care should be taken when considering the use of low moisture grades or dried MCC in a direct compression formulation which contains a large proportion of poorly compressible materials [19]. Since much of the moisture sorbed under ambient conditions has been shown to be bound to the MCC particles [16,17], the use of dried MCC to improve drug stability in tableting moisture sensitive drugs is also of limited value.

Although not a marketed grade, ground MCC has inferior compaction properties when compared with the unground material [26]. However grinding a poorly soluble drug with MCC can result in improved dissolution and absorption characteristics of the drug [27].

Section 4: Comparative Properties of Various Commercial Forms of MCC

As stated previously, newer commercial forms of MCC have recently been introduced. Although most achieve compendial specifications, this does not necessarily mean equivalent performance during tableting. It is of obvious interest to the formulator to know the differences between materials, and the advantages or disadvantages of using one of these newer materials

instead of Avicel either in developmental or existing formulations. Unfortunately, little independently derived information regarding the use of the newer commercial forms of MCC has been published. The results of the work which have been reported, and some of the reasons for the differences will be discussed here.

A comprehensive study concerning the comparative properties of 7 commercial forms of MCC comparable to Avicel PH-101 (type 1 materials) and 5 materials comparable to Avicel PH-102 (type 2 materials) has been reported by Doelker et al [23]. In some cases, more than one batch of a material was studied to investigate batch to batch uniformity. Some differences between materials were found with respect to particle properties such as moisture content, particle size distribution, and with characteristics related to packing and flow. The Avicels performed well overall with respect to compactability with and without magnesium stearate, and exhibited good disintegration properties. Some materials exhibited significantly inferior properties, although it shuld be noted that inter-batch variations, even with the Avicels were found. In conclusion, the authors stated no single MCC material universally exhibited the best properties in each category and that the performance of some of the newer materials was comparable to that of the Avicels.

A study by Whiteman and Yarwood considered some differences in powder characteristics and the tableting perfomance of some MCC meterials mixed with 0.5% magnesium stearate and 3.4% crospovidone [24]. Again, the performance of some of the commercial forms was significantly different, in most cases inferior, to that of the Avicels. The authors also found tablet weight variation and compression characteristics could not be predicted by simple tests on the powder materials. Hence it was suggested that compaction profiles should be included in in-house specifications for MCC, particularly if the intention is to use it in formulations prepared by direct compression.

In both studies, differences between tableting characteristics and commercial forms of MCC were suggested to be due to differences in particle structure arising from variations in the manufacturing process [23,24]. If differences resulted in particles having an increased ability to undergo plastic deformation, the material would have a greater compressibility [23]. In this context, the importance of degree of crystallinity and the degree of polymerisation was investigated [23,28]. Although differences in the two parameters were found between the commercial forms of MCC [28], in some unpublished work the crystallinity or morphology of particles could not be correlated with tableting properties [23]. Hence, the reasons for the differences between commercial forms of MCC is still open question.

Particular interest can be found in the literature concerning Emcocel, the MCC material produced by Mendell. Of the MCC materials studied by Whiteman and Yarwood, Emcocel had the compaction profile most like Avicel PH-101 [24], and in the study by Doelker et al, Emcocel and Emcocel 90M compared favourably overall with Avicel PH-101 and PH-102 respectively [23]. Other workers have also compared the properties of Emcocel to Avicel PH-101 [20,29,30,31].

Paronen and Pesonen found the performance of the two materials in direct compression to be very similar and concluded neither were superior [29]. Their results also suggest Emcocel can be used in equal quantities to replace the Avicel content in direct compression formulations. Some differences between the two materials have however been found in relation

to the properties of the material after granulation [20]. Avicel was found to exhibit a greater degree of loss of compactability than Emcocel when granulated with 37% w/w water [20]. Some of the comparatative properties between Avicel PH-101 and Emcocel are shown in Table 2. It should be noted that apart for Avicel PH-101 in the study by Doelker et al [23] batch to batch uniformity has not been considered, and some of the differences between the two materials may lie within inter-batch variations. Thus differences between one batch of Avicel and one of Emcocel may be less than that found between, for example, two different batches of Avicel.

In conclusion, the unique physico-chemical properties of cellulose, and the enhanced physico-mechanical properties of mirocrystalline cellulose provide a tableting excipient with very wide applications, both in direct compression and granulated systems. It should be noted that the characteristics of different grades and the potential differences between commercial forms should be taken into account when considering the use of MCC in a specific formulation.

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TABLE 1 Summary of some of the differences between the Avicel PH-grades

*Qualitative Description

Avicel grade	Median particle diameter (μm) - Coulter counter method [21]	Particle size analysis [8] Mesh Size	Percent Retained	Specific surface area by nitrogen adsorption ($m^2 g^{-1}$) [17]	Moisture Specification [6]	*Flow Characteristics [6]	*Strength of tablets prepared under similar conditions	*Disintegration properties and dissolution rate from tablets [25]
PH-101	49.5	60	<1.0	1.22	<5.0%	Acceptable	Slightly stronger tablets than from PH-102 [24]	Good
		200	<30.0					
PH-102	85.5	60	<8.0	1.12	<5.0%	Very good	Slightly weaker tablets than from PH-101 [24]	Good
		200	<45.0					
PH-103	46	60	<1.0	-	<3.0%	Acceptable	Tablets expected to be weaker than those from PH-101 [18,19]	Good
		200	<30.0					
PH-105	16.5	60	<0.1	2.45	<5.0%	Poor	-	Relatively poor
		400	<1.0					

TABLE 2 Some qualitative comparisons between the properties of two commercial forms of MCC; Avicel PH-101 and Emcocel

Characteristic	Difference noted between Avicel PH-101 and Emcocel	Reference
Particle shape	Mean shape of both is a thin dendrite Emcocel particles slightly more circular and less irregular than those of Avicel	[29,30]
Particle size and size distribution	Emcocel has a greater number of both very small and large particles than Avicel, hence a larger size distribution	[29]
Crystallinity index	Emcocel particles are slightly more crystalline than Avicel particles	[29]
Moisture content	Except for one study [29], Emcocel was found to contain slightly more moisture than Avicel	[23,24, 31]
Powder characteristics related to flow properties of powder	Both materials have fair flowability and are moderately cohesive. If anything, Emcocel has slightly superior flow and exhibits less interparticulate cohesion	[24,29 31]
Coefficient of tablet weight variation from lubricated powders	Approximately similar for the two materials	[23,24 29]
Tablet strength of unlubricated and lubricated powders prepared at similar compaction pressures	Strength of tablets from unlubricated powders similar	[23,29]
	When lubricated, Emcocel produced slightly weaker tablets than Avicel	[23,24]
Binding properties	Comparable for the two materials	[29]
Disintegration properties	Comparable for the two materials	[23]
Compactibility of a wet granulation prepared with 37% water	Emcocel exhibited a lower degree of loss of compactability, ie. produced stronger tablets than Avicel after granulation	[20]

Figure 1 The Cellulose Molecule ($n \approx$ 1,000 to 15,000)

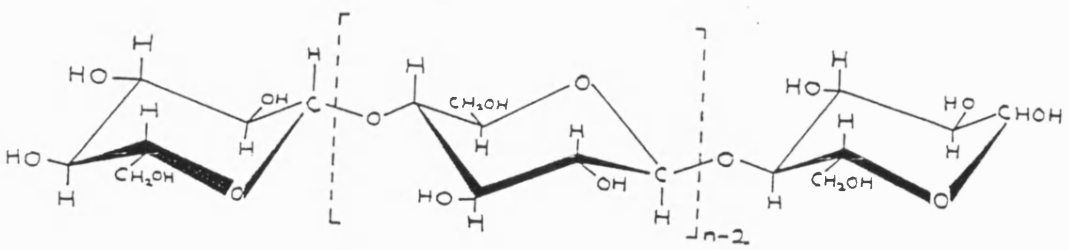


Figure 2 Schematic diagram of the structure of a wood fibre

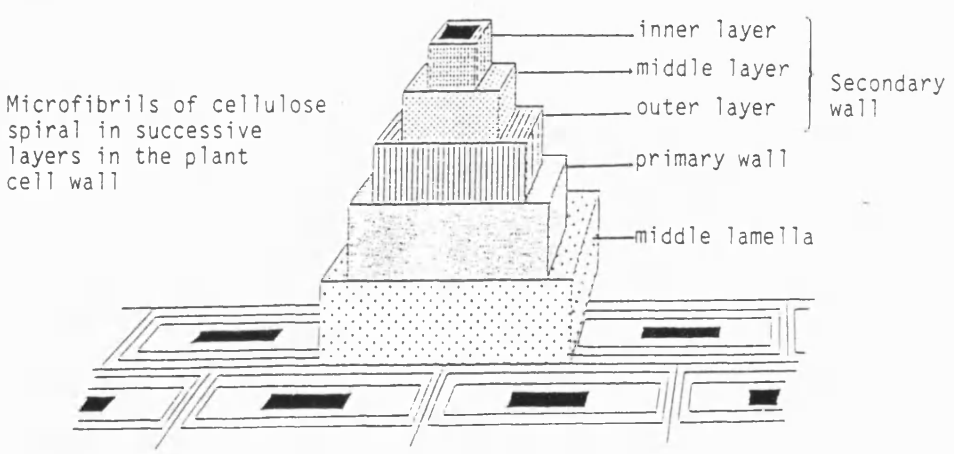


Figure 3a

Schematic diagram indicating the intramolecular hydrogen bonds which are responsible for the rigidity of cellulose molecules, and intermolecular hydrogen-bonds which hold adjacent chains together as 'sheets'.

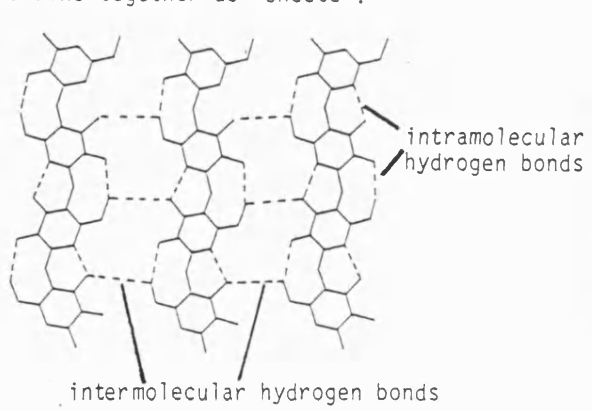


Figure 3b

Schematic diagram showing the stacking arrangement of cellulose 'sheets'. Attraction between successive sheets results from Van der Waals forces.

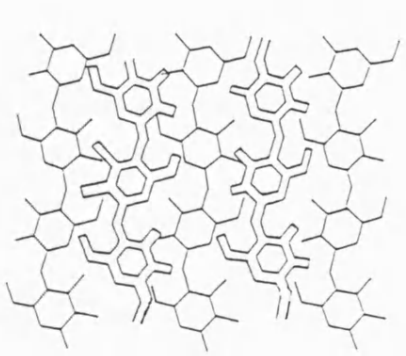


Figure 4 The structure of a cellulose microfibril according to the fringe micellar theory.

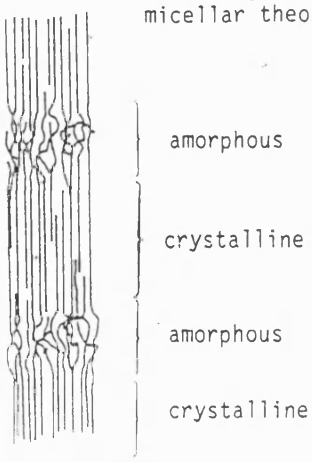


Figure 5 Single phase model of the structure of a cellulose microfibril.

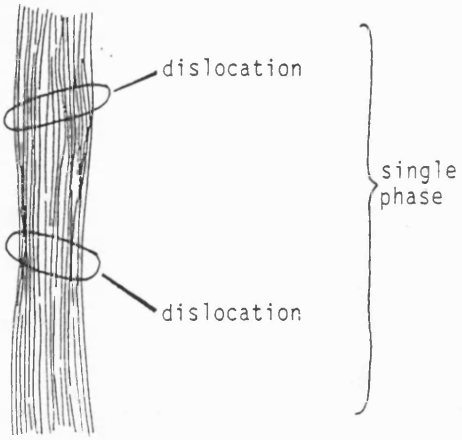
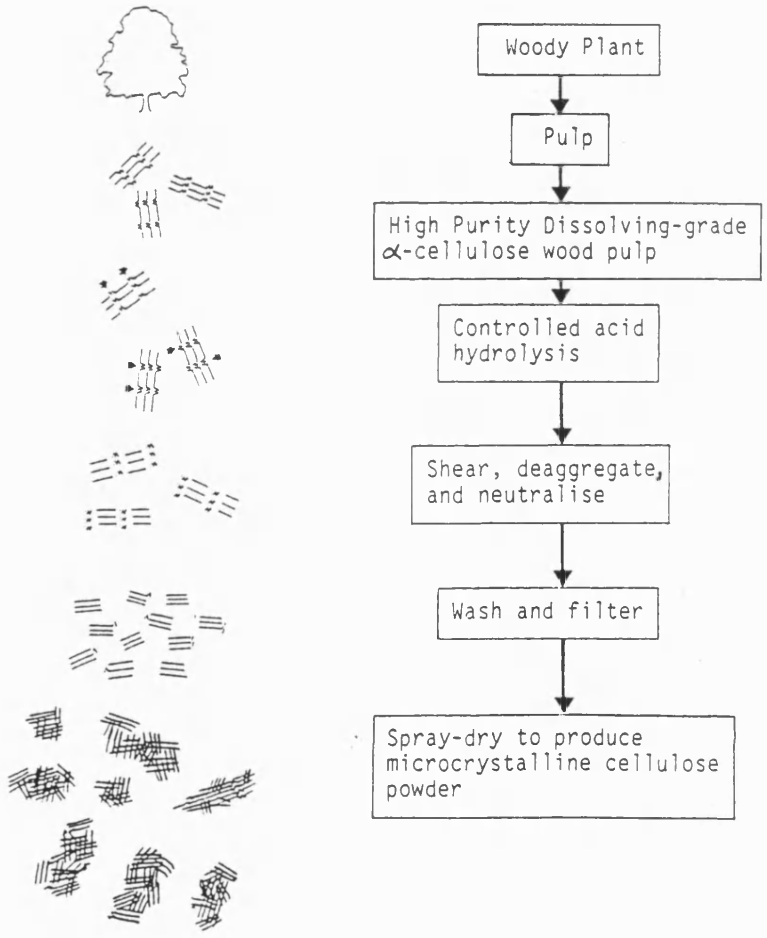


Figure 6 Schematic diagram showing the stages involved in the manufacture of microcrystalline cellulose.



Appendix ii. Data for calculation of the solubility (cohesion) parameters of ungranulated and granulated MCC

Table ii.1. Retention times (t_r, min) of adsorbates on ungranulated MCC at a series of temperatures (T, K) from gas - solid chromatography. The dead time for the column at each temperature is presented in bold (t_m, min), and was calculated from the retention times of the alkanes using equation 8.5.

T(K)	pent	hex	hep	oct	non	dec	ACN	meth	eth	prop	CCl_4	t_m
[1]312	0.44	0.48	0.77	1.51	4.00	9.55	0.87	1.73	1.24	1.60	0.57	**0.35**
[1]322	0.41	0.44	0.64	1.09	2.90	6.60	0.76	1.20	0.85	1.15	0.47	**0.31**
[2]332	0.39	0.41	0.51	0.74	1.47	3.25	0.61	1.02	0.60	0.74	0.44	**0.36**
[2]343	0.36	0.40	0.46	0.62	0.99	2.38	0.55	1.00	0.58	0.59	0.40	**0.34**
[2]349	0.38	0.42	0.47	0.63	0.89	1.75	0.53	0.95	0.51	0.56	0.40	**0.37**
[2]355	0.37	0.38	0.43	0.53	0.79	1.50	0.52	0.88	0.48	0.51	0.39	**0.36**
[2]360	0.37	0.39	0.41	0.51	0.71	1.18	0.50	0.84	0.46	0.49	0.40	**0.36**
[2]365	0.38	0.40	0.42	0.49	0.66	1.00	0.48	0.74	0.45	0.47	0.39	**0.37**

Experimental conditions under which retention times were obtained (the experimental conditions were determined at each column temperature and were presumed not to alter between measurements using different adsorbates at each temperature):

[1] flow rate measured by soap bubble flowmeter: 15.38×10^{-6} m^3min^{-1}
Ambient temperature: 298 K
Inlet pressure: 199.6×10^3 Nm^{-2}
Outlet pressure / atmospheric pressure: 99.6×10^3 N m^{-2}
Mass of stationary phase: 1.4876×10^{-3} kg

[2] flow rate measured by soap bubble flowmeter: 15.79×10^{-6} m^3min^{-1}
Ambient temperature: 298 K
Inlet pressure: 198.9×10^3 Nm^{-2}
Outlet pressure / atmospheric pressure: 98.9×10^3 Nm^{-2}
Mass of stationary phase: 1.4876×10^{-3} kg

Note: pent = pentane, hex = hexane, hep = heptane, oct = octane, non = nonane, dec = decane, ACN = acetonitrile, meth = methanol, eth = ethanol, prop = propan-1-ol, CCl_4 = carbontetrachloride

Table ii.2. Corrected retention times (t'_r min) and in bold the specific volume of retention ($V'_{g(Tc)}$ x 10^{-3} m^3kg^{-1}), for adsorbates on ungranulated MCC at different temperatures (T, K) obtained from gas - solid chromatography.

T(K)	pent	hex	hep	oct	non	dec	ACN	meth	eth	prop	CCl_4
[1]312	0.09	0.13	0.42	1.16	3.65	9.20	0.52	1.38	0.89	1.25	0.22
	0.625	**0.903**	**2.918**	**8.061**	**25.36**	**64.07**	**3.597**	**9.583**	**6.172**	**8.671**	**1.529**
[1]322	0.10	0.13	0.33	0.78	2.59	6.29	0.45	0.89	0.54	0.84	0.16
	0.717	**0.932**	**2.366**	**5.585**	**18.54**	**45.15**	**3.222**	**6.360**	**3.857**	**6.050**	**1.147**
[2]332	0.03	0.05	0.15	0.38	1.11	2.89	0.25	0.66	0.24	0.38	0.08
	0.227	**0.378**	**1.135**	**2.886**	**8.415**	**21.87**	**1.893**	**5.003**	**1.822**	**2.875**	**0.607**
[2]343	0.02	0.06	0.12	0.28	0.65	2.04	0.21	0.66	0.24	0.25	0.06
	0.156	**0.469**	**0.938**	**2.181**	**5.084**	**15.96**	**1.642**	**5.155**	**1.878**	**1.954**	**0.468**
[2]349	0.01	0.05	0.10	0.26	0.52	1.38	0.16	0.58	0.14	0.19	0.03
	0.078	**0.399**	**0.796**	**2.075**	**4.137**	**10.98**	**1.273**	**4.618**	**1.114**	**1.511**	**0.239**
[2]355	0.01	0.02	0.07	0.17	0.43	1.14	0.16	0.52	0.12	0.15	0.03
	0.081	**0.162**	**0.567**	**1.376**	**3.490**	**9.226**	**1.296**	**4.221**	**0.971**	**1.214**	**0.242**
[2]360	0.01	0.03	0.05	0.15	0.25	0.82	0.14	0.48	0.10	0.13	0.04
	0.082	**0.247**	**0.411**	**1.231**	**2.052**	**6.733**	**1.149**	**3.935**	**0.821**	**1.067**	**0.320**
[2]365	0.01	0.03	0.05	0.12	0.29	0.63	0.11	0.37	0.08	0.10	0.02
	0.083	**0.249**	**0.414**	**0.999**	**2.411**	**5.244**	**0.916**	**3.065**	**0.666**	**0.835**	**0.167**
*grad	5769	3330	4406	4405	5491	5354	2911	1972	4637	5061	8028
**SE	726	731	298	218	335	212	220	256	336	191	612
***r	0.949	0.886	0.988	0.993	0.989	0.996	0.984	0.957	0.987	0.996	0.952

*grad is the gradient, **SE is the standard error of the gradient, and ***r the correlation coefficient from linear regression analysis of ln $V'_{g(Tc)}$ against $1/T_c$. From equation 8.7, the gradient is equal to $-\Delta E^A/R$, where $-\Delta E^A$ is the adsorption energy (J mol^{-1}) of the solvent onto ungranulated MCC, and R (8.314 $JK^{-1}mol^{-1}$) is the universal gas constant.

[1] and [2] denote experimental conditions under which retention times were obtained (see table ii.1). The conditions were presumed not to alter between measurements using different adsorbates at each temperature.

Note: pent = pentane, hex = hexane, hep = heptane, oct = octane, non = nonane, dec = decane, ACN = acetonitrile, meth = methanol, eth = ethanol, prop = propan-1-ol, CCl_4 = carbontetrachloride

Table ii.3. Retention times (t_r, min) of adsorbates on granulated MCC at a series of temperatures (T, K) from gas - solid chromatography. The dead time for the column at each temperature is presented in bold (t_m, min), and was calculated from the retention times of the alkanes using equation 8.5.

T(K)	pent	hex	hep	oct	non	dec	ACN	meth	eth	prop	CCl_4	t_m
[1]312	0.28	0.32	0.39	0.64	1.64	3.40	0.44	0.59	0.52	0.71	0.32	**0.25**
[1]322	0.28	0.30	0.35	0.51	0.95	2.10	0.37	0.48	0.42	0.54	0.32	**0.25**
[1]332	0.27	0.31	0.32	0.42	0.70	1.56	0.35	0.46	0.38	0.41	0.30	**0.24**
[1]343	0.28	0.29	0.33	0.39	0.58	1.05	0.33	0.44	0.34	0.36	0.29	**0.26**
[2]349	0.27	0.29	0.30	0.36	0.49	0.82	0.32	0.42	0.32	0.34	0.28	**0.26**
[2]355	0.27	0.29	0.30	0.35	0.45	0.69	0.32	0.37	0.32	0.33	0.27	**0.26**
[2]360	0.27	0.27	0.29	0.33	0.42	0.60	0.31	0.35	0.30	0.32	0.27	**0.26**
[2]365	0.27	0.27	0.28	0.31	0.39	0.54	0.30	0.32	0.28	0.30	0.27	**0.26**

Experimental conditions under which retention times were obtained (the experimental conditions were determined at each column temperature and were presumed not to alter between measurements using different adsorbates at each temperature):

[1] flow rate measured by soap bubble flowmeter: 14.29×10^{-6} m^3min^{-1}
Ambient temperature: 294 K
Inlet pressure: 154.9×10^3 Nm^{-2}
Outlet pressure / atmospheric pressure: 99.9×10^3 Nm^{-2}
Mass of stationary phase: 2.068×10^{-3} kg

[2] flow rate measured by soap bubble flowmeter: 13.64×10^{-6} m^3min^{-1}
Ambient temperature: 296 K
Inlet pressure: 155.6×10^3 Nm^{-2}
Outlet pressure / atmospheric pressure: 100.6×10^3 Nm^{-2}
Mass of stationary phase: 2.068×10^{-3} kg

Note: pent = pentane, hex = hexane, hep = heptane, oct = octane, non = nonane, dec = decane, ACN = acetonitrile, meth = methanol, eth = ethanol, prop = propan-1-ol, CCl_4 = carbontetrachloride

Table ii.4. Corrected retention times (t'_r min) and in bold the specific volume of retention ($V_{g(Tc)}$ x 10^{-3} m^3kg^{-1}), for adsorbates on granulated MCC at different temperatures (T', K) obtained from gas - solid chromatography.

T(K)	pent	hex	hep	oct	non	dec	ACN	meth	eth	prop	CCl_4
[1]312	0.03	0.07	0.14	0.39	1.39	3.15	0.19	0.34	0.27	0.46	0.07
	0.167	**0.396**	**0.792**	**2.207**	**7.868**	**17.83**	**1.076**	**1.925**	**1.528**	**2.604**	**0.396**
[1]322	0.03	0.05	0.10	0.26	0.70	1.85	0.12	0.23	0.17	0.29	0.07
	0.175	**0.292**	**0.584**	**1.519**	**4.088**	**10.80**	**0.701**	**1.343**	**1.007**	**1.694**	**0.409**
[1]332	0.03	0.07	0.08	0.18	0.46	1.32	0.11	0.22	0.14	0.17	0.06
	0.181	**0.421**	**0.482**	**1.084**	**2.770**	**7.949**	**0.662**	**1.324**	**0.843**	**1.024**	**0.361**
[1]343	0.02	0.03	0.07	0.13	0.32	0.79	0.07	0.17	0.08	0.10	0.03
	0.124	**0.187**	**0.405**	**0.809**	**1.992**	**4.914**	**0.436**	**1.058**	**0.498**	**0.623**	**0.187**
[2]349	0.01	0.03	0.04	0.10	0.23	0.56	0.06	0.16	0.06	0.08	0.02
	0.060	**0.181**	**0.241**	**1.662**	**1.384**	**3.370**	**0.361**	**0.963**	**0.361**	**0.481**	**0.120**
[2]355	0.01	0.03	0.04	0.09	0.19	0.43	0.06	0.11	0.06	0.07	0.01
	0.061	**0.184**	**0.245**	**0.551**	**1.163**	**2.633**	**0.367**	**0.673**	**0.368**	**0.428**	**0.061**
[2]360	0.01	0.01	0.03	0.07	0.16	0.34	0.05	0.09	0.04	0.06	0.01
	0.062	**0.062**	**0.186**	**0.434**	**1.007**	**2.111**	**0.279**	**0.559**	**0.248**	**0.372**	**0.062**
[2]365	0.01	0.01	0.02	0.05	0.13	0.28	0.04	0.06	0.02	0.04	0.01
	0.063	**0.063**	**0.126**	**0.315**	**0.819**	**1.763**	**0.252**	**0.378**	**0.126**	**0.252**	**0.063**
*grad	3850	3850	3587	3923	4673	4985	2987	3019	4710	4825	4887
**SE	605	943	400	219	164	173	197	460	548	165	739
***r	0.881	0.858	0.963	0.993	0.997	0.996	0.986	0.939	0.983	0.996	0.938

*grad is the gradient, **SE is the standard error of the gradient, and ***r the correlation coefficient from linear regression analysis of ln $V'_{g(Tc)}$ against $1/T_c$. From equation 8.7, the gradient is equal to $-\Delta E^A/R$, where $-\Delta E^A$ is the adsorption energy (J mol^{-1}) of the solvent onto ungranulated MCC, and R (8.314 $JK^{-1}mol^{-1}$) is the universal gas constant.

[1] and [2] denote experimental conditions under which retention times were obtained (see table ii.3). The conditions were presumed not to alter between measurements using different adsorbates at each temperature.

Note: pent = pentane, hex = hexane, hep = heptane, oct = octane, non = nonane, dec = decane, ACN = acetonitrile, meth = methanol, eth = ethanol, prop = propan-1-ol, CCl_4 = carbontetrachloride

Appendix iii

iii.1 Calculation of the volume of moisture adsorbed onto ungranulated and granulated MCC as a function of the relative water vapour pressure.

Previously determined volumes for apparatus in figure 10.1:-

Volume between taps C and D = 98.5 cm^3

Volume of the calorimeter cells and tubespace upto tap D = 66.4 cm^3

Total volume between tap C and the calorimeter cells = 164.9 cm^3

Knowing the deadspace volume of the apparatus, the volumes of water vapour admitted and adsorbed may be obtained from the pressure measurements using Boyles Law:-

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2}$$

Where P, V and T are the pressure, volume and temperature of the water vapour respectively under specified conditions 1 and 2.

Defining conditions 1 as P_1 = 760 mm Hg, and T_1 = 273.2 K, and conditions 2 as the experimental conditions under which the dose pressures were determined, that is where T_2 = 295.7 K, from Boyle's Law $V_1 = 0.001216\ P_2\ V_2$

Knowing the apparatus volumes:

If the dose pressure (mm Hg) is taken as the pressure exerted by a dose of water vapour in the space been taps C and D as recorded by the pressure gauge immediately before admission into calorimeter cells then:-

dose volume (cm^3) = 0.001216 x dose pressure x 98.5

Further, if the final pressure (mm Hg) is taken as the vapour pressure of this dose of water vapour following equilibration with the sample and occupying the space from tap C to the calorimeter cells (corrected as described in section 10.2.), then:-

final volume (cm^3) = 0.001216 x final pressure x 164.9

The volume of water vapour remaining in the space from tap D to the calorimeter cells from the previous dose may be determined from the following relationship:

$$\text{Remainder volume } (cm^3) = 0.001216 \times \text{previous final pressure} \times 66.4$$

The volume of water vapour adsorbed for each dose, V_{ads} (cm^3), is the difference between the volume of water vapour in the system before and after equilibration with the sample, which equals dose volume + remainder volume - final volume (all at conditions 1 defined above).

By summing the volume adsorbed following equilibration with successive doses of water vapour up to the required vapour pressure, the total volume of water vapour adsorbed under conditions defined as 1 above for each dose, (Total V_{ads}), may be determined.

The heat evolved as a result of equilibration with individual doses of water vapour may be converted into heat evolved per mole of water vapour adsorbed under conditions 1 from the following relationship;

$$\text{Heat evolved } (kJ\ mol^{-1}) = \frac{\text{heat evolved (kJ)} \times \text{gas molar volume under conditions 1 } (22400\ cm^3)}{\text{volume adsorbed under conditions 1 } (cm^3)}$$

iii.2 Results

Table iii.1. Experimental (in bold) and calculated data for the volumes adsorbed and heat evolved resulting from equilibration of ungranulated MCC with successive doses of water vapour.

Sample weight = 0.0972g

Saturated water vapour pressure at 30°C = 31.84 mm Hg

Dose	Dose P. (mm Hg)	Final P. (mm Hg)	Dose Vol. (cm^3)	Remainder Vol. (cm^3)	Final Vol. (cm^3)	ΔV_{ads} (cm^3)	Total V_{ads} (cm^3)	Total V_{ads} (µmol)	Total V_{ads} (mole water per 100g solid)	Heat evolved (mJ)	Heat of adsorption ($kJ\ mol^{-1}$)	Relative pressure
1	1.072	0.053	0.1284	0.0000	0.0106	0.1178	0.1178	5.269	0.0054	420	80	0.0016
2	0.944	0.093	0.1131	0.0043	0.0186	0.0988	0.2166	9.670	0.0100	322	73	0.0029
3	1.143	0.145	0.1369	0.0075	0.0291	0.1153	0.3319	14.82	0.0152	343	66	0.0045
4	1.231	0.217	0.1475	0.0117	0.0435	0.1157	0.4476	19.98	0.0206	328	64	0.0068
5	1.561	0.323	0.1870	0.0175	0.0648	0.1397	0.5873	26.22	0.0270	390	63	0.0101
6	1.304	0.376	0.1562	0.0261	0.0754	0.1069	0.6942	30.99	0.0319	250	52	0.0118
7	1.573	0.497	0.1884	0.0303	0.0996	0.1191	0.8133	36.31	0.0374	312	59	0.0156
8	1.829	0.642	0.2191	0.0401	0.1287	0.1305	0.9438	42.13	0.0433	334	57	0.0202
9	1.606	0.743	0.1924	0.0518	0.1490	0.0952	1.039	46.38	0.0477	233	55	0.0233
10	1.799	0.858	0.2155	0.0600	0.1720	0.1035	1.143	51.03	0.0525	245	53	0.0269
11	1.418	0.886	0.1699	0.0692	0.1776	0.0615	1.204	53.75	0.0553	102	37	0.0278
12	1.907	1.014	0.2285	0.0715	0.2033	0.0967	1.300	58.04	0.0597	223	52	0.0318
13	1.654	1.080	0.1981	0.0818	0.2165	0.0634	1.363	60.85	0.0626	128	45	0.0339
14	1.613	1.088	0.1932	0.0872	0.2181	0.0628	1.425	63.62	0.0655	75	27	0.0342
15	2.85	1.32	0.341	0.088	0.265	0.164	1.589	70.84	0.0729	372	51	0.0415
16	3.94	1.78	0.472	0.106	0.357	0.221	1.810	80.80	0.0831	558	57	0.0558
17	5.22	2.40	0.625	0.144	0.481	0.288	2.098	93.66	0.0964	738	57	0.0754
18	6.54	3.15	0.783	0.194	0.632	0.345	2.443	109.1	0.1122	855	56	0.0989
19	6.91	3.89	0.828	0.254	0.780	0.302	2.745	122.5	0.1260	755	56	0.1222
20	8.50	4.87	1.018	0.314	0.976	0.356	3.101	138.4	0.1423	890	56	0.1530

Table iii.2. Experimental (in bold) and calculated data for the volumes adsorbed and heat evolved resulting from equilibration of granulated MCC with successive doses of water vapour.

Sample weight = 0.0996 g

Saturated water vapour pressure at 30°C = 31.84 mm Hg

Dose	Dose P. (mm Hg)	Final P. (mm Hg)	Dose Vol. (cm^3)	Remainder Vol. (cm^3)	Final Vol. (cm^3)	ΔV_{ads} (cm^3)	Total V_{ads} (cm^3)	Total V_{ads} (μmol)	Total V_{ads} (mole water per 100g solid)	Heat evolved (mJ)	Heat of adsorption ($kJ\ mol^{-1}$)	Relative pressure
1	0.762	0.043	0.0913	0.0000	0.0086	0.0827	0.0827	3.692	0.0037	280	76	0.0014
2	1.367	0.134	0.1638	0.0035	0.0269	0.1404	0.2231	9.960	0.0100	433	69	0.0042
3	1.240	1.198	0.1486	0.0108	0.0397	0.1197	0.3428	15.30	0.0154	339	63	0.0062
4	1.600	0.315	0.1917	0.0160	0.0623	0.1445	0.4873	21.75	0.0218	411	64	0.0099
5	1.407	0.399	0.1687	0.0254	0.0800	0.1141	0.6014	26.85	0.0270	309	61	0.0125
6	1.438	0.665	0.1723	0.0322	0.1333	0.0712	0.6726	30.03	0.0304	279	88	0.0209
7	1.807	0.670	0.2165	0.0537	0.1343	0.1323	0.8085	36.09	0.0362	363	60	0.0210
8	1.925	0.760	0.2306	0.0541	0.1524	0.1323	0.9408	42.00	0.0422	345	58	0.0239
9	2.003	0.872	0.2400	0.0613	0.1748	0.1265	1.0673	47.65	0.0478	320	57	0.0274
10	1.820	0.934	0.2180	0.0704	0.1873	0.1011	1.1684	52.16	0.0523	220	49	0.0293
11	1.730	1.013	0.2073	0.0754	0.2031	0.0796	1.248	55.71	0.0559	182	51	0.0318
12	1.734	1.085	0.2077	0.0817	0.2175	0.0719	1.320	58.93	0.0592	155	48	0.0341
13	1.531	1.060	0.1834	0.0876	0.2125	0.0585	1.379	61.56	0.0618	70	27	0.0333
14	2.37	1.22	0.284	0.0855	0.245	0.124	1.503	67.10	0.0674	257	46	0.0385
15	3.69	1.67	0.442	0.098	0.335	0.205	1.708	76.25	0.0766	513	56	0.0524
16	4.84	2.20	0.580	0.135	0.441	0.274	1.982	88.48	0.0889	677	55	0.0691
17	5.79	2.80	0.694	0.178	0.561	0.311	2.293	102.37	0.1028	745	54	0.0879
18	6.98	3.57	0.830	0.226	0.716	0.340	2.633	117.54	0.1180	834	55	0.1121
19	8.06	4.54	0.966	0.288	0.910	0.344	2.977	132.90	0.1334	872	57	0.1426